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Update on the Use of Tacrolimus in Pediatrics

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Tacrolimus is one of the most widely used immunosuppressive agents following solid organ transplantation. Tacrolimus is a macrolide isolated from the soil bacterium *Streptomyces tsukubaensis*.[1] It exerts its effect by binding to the receptor FK binding protein, inhibiting the phosphatase activity of calcineurin. This interferes with the transcription of cytokines required for the activation and proliferation of T lymphocytes.[2,3] Prograf ® (tacrolimus) was first approved for use by the Food and Drug Administration (FDA) in 1994 for prophylaxis of organ rejection in patients receiving allogenic liver transplants. This approval was expanded in 2006 to include heart transplant recipients, and later in 2009 to include kidney transplant recipients.

In 2013 an extended release formulation, Astagraf XL™, was FDA approved for the prophylaxis of organ rejection in adult kidney transplant patients when used in combination with other immunosuppressant medications. Later, in 2015, Envarsus XR® was approved by the FDA for prophylaxis of organ rejection in adult kidney transplant patients converted from tacrolimus immediate release formulation in combination with other immunosuppressants. Due to the variety of available dosage forms, emerging data on optimal dosing, and novel uses for tacrolimus, this issue provides an update for clinicians who care for patients treated with tacrolimus.

Pharmacokinetics

It is critical for patients to achieve optimal immunosuppression in the first days following solid organ transplantation to avoid rejection. Tacrolimus has a narrow therapeutic index, making it challenging for patients to achieve therapeutic dosing while avoiding adverse effects. Measurement of the area under the curve (AUC) would be the most effective way of measuring tacrolimus concentrations, however, this is not always feasible for patients or institutions. Whole blood trough levels correlate with the AUC and are more commonly used to monitor tacrolimus.[4]

Tacrolimus absorption occurs primarily in the small intestine. The differences in intestinal P-glycoprotein (PGP) and intestinal motility in children can account for some of the variability in absorption. Tacrolimus distributes widely throughout the body to the lungs, spleen, liver, kidney, brain and muscle. It is highly protein bound to alpha 1-acid-gycoprotein and, to a lesser extent, albumin. Pediatric patients have a reduced drug binding affinity of plasma proteins, leading to an increased fraction of unbound drug. This can cause an increased distribution and elimination of free drug, and higher doses of tacrolimus may be needed to achieve the same concentration range.

Tacrolimus is metabolized primarily via cytochrome P450 3A5 (CYP3A5). Activity of this hepatic enzyme is age-dependent and may not be fully developed in younger children. Tacrolimus is also a substrate of PGP, an efflux pump encoded by multidrug resistance 1 gene (MDR1 or ABCB1). This gene contributes to tacrolimus metabolism, producing inactive metabolites, but to a lesser extent.[5] These two modes of metabolism may account for the pharmacokinetic variation in tacrolimus seen between adults and children.[6]

Pharmacogenomics

Given the narrow therapeutic index, personalized medicine can be beneficial with the use of tacrolimus. Single nucleotide polymorphisms (SNPs) in the CYP3A5 gene can influence tacrolimus drug concentrations.[5] The mutation of G6986A produces the CYP3A5*3 allele. Those who are homozygotes for CYP3A5*3 (CYP3A5*3/*3) are considered non-expressers, and lose their functional enzyme. Expression of CYP3A5*1 (CYP3A5*1/*1, CYP3A5*1/3) leads to a higher enzymatic activity and metabolism of tacrolimus.[7] CYP3A5*1 expressers may require

two-fold higher doses of tacrolimus to achieve therapeutic blood targets.[5]

In May 2018, a study by Min and colleagues evaluated a new way of dosing tacrolimus based on a patient's genotype. They compared genotype-guided dosing to standard dosing of tacrolimus in pediatric patients receiving heart, kidney, or liver transplant. The goal was to compare time to achieve and maintain therapeutic tacrolimus trough concentrations between the two groups. Patients were categorized as being CYP3A5 expressers or non-expressers, then randomized after transplantation to receive either genotype-guided dosing (n=35) or standard dosing (n=18) for tacrolimus. Those who were in the genotype-guided dosing group were dosed based on a sliding scale algorithm, with the lowest dose in older patients (more than 6 years of age) who were CYP3A5 non-expressers and the highest dose in younger children (less than 6 years) who were CYP3A5 expressers. Patients were followed for 30 days after initiation.

Patients in the genotype-guided dosing arm achieved therapeutic tacrolimus concentrations earlier than those in the standard clinical dosing arm, with the median time to first therapeutic concentration of 3.4 (range 2.5-6.6) days in the genotype-guided arm and 4.7 (3.5-8.6) days in the standard arm (p=0.049). In the genotype-guided group, 69% of patients achieved stable tacrolimus concentrations, while only 44% of patients in the standard arm achieved stable concentrations within 30 days (p=0.089).

The median time to achieve stable therapeutic concentrations was 18 (range 14-27) days in the genotype-guided arm. This median time could not be calculated in the standard arm because < 50% of participants achieved stable therapeutic concentrations during study follow-up.[5] This study indicates that genotype-guided dosing could be a favorable approach to tacrolimus initiation.

Dosage Forms

Tacrolimus is commercially available in the United States as an immediate release oral capsule and IV formulation (Prograf®), an extended release capsule (Astagraf XL™), and an extended release tablet (Envarsus XR®). The contents of the immediate release capsule can also be compounded to form an oral suspension. In adult patients, the dosing conversions between agents are defined. If patients are converted from the immediate release oral formulation to the IV formulation, the oral dose is multiplied by ¼ to obtain the IV dose. When switching from an immediate release formulation of tacrolimus to Astagraf XL™, the dose conversion is 1:1. When switching from an immediate release formulation to Envarsus XR®, the dosing conversion is less straightforward, and is more similar to a 1:0.75 conversion, where 0.75 represents the Envarsus XR® formulation.

Recently, several studies analyzed the pharmacokinetics of switching from immediate release to extended release formulations of tacrolimus in pediatric patients. Lapeyraque and colleagues analyzed the conversion from twice daily immediate release tacrolimus to once daily Advagraf® (approved in Europe, listed as a 1:1 conversion in adults) in pediatric renal transplant patients between 6-20 years of age. Patients were converted on a 1:1 basis from their current total daily dose. AUC studies were performed over 24 hours by taking a blood sample immediately before drug administration and at a variety of time points after drug administration. The median total daily baseline tacrolimus dose was 0.11 mg/kg. The median AUC of twice daily dosing was 222.3 ng/mL compared to 197.5 ng/mL in daily dosing ($p = 0.03$). The median minimum concentration (C_{min}) of twice daily dosing was 6.5 ng/mL, which was significantly higher than the C_{min} for daily dosing of 5.6 ng/mL ($p = 0.01$). This study demonstrated that a 1:1 conversion from twice-daily to daily tacrolimus resulted in a sustained decrease in tacrolimus exposure as shown by a lower AUC and C_{min}.[8] This indicates that when converting from twice-daily to daily tacrolimus regimens based on the current total daily dose, increased monitoring of drug levels is necessary to ensure therapeutic levels are maintained.

Quintero and colleagues evaluated the safety and efficacy of converting from twice daily to once daily tacrolimus in pediatric liver transplant patients. Patients were converted on a 1:1 basis from their current total daily dose. After conversion, doses were adjusted to maintain target trough levels. The mean daily tacrolimus dose was 0.09 mg/kg pre-conversion, with a significant increase to a mean of 0.11 mg/kg at three months after conversion ($p < 0.001$). Thirty-five of the 55 (63.6%) patients needed modification of their original tacrolimus dose to maintain plasma trough levels during the first year after conversion. The average increase in dose was 0.013 mg/kg, representing an increase of 14.8% of the pre-conversion dose.[9] Patients were shown to have better adherence and similar safety profile post conversion. Both of these studies indicate that when converting pediatric patients from immediate to prolonged release tacrolimus, dose modifications may be required.

In February 2018, the first study was performed that randomized de novo pediatric patients to receive immediate release or prolonged release tacrolimus. The study included 44 pediatric patients undergoing kidney, liver or heart transplantation. Patients were randomized to receive either prolonged release tacrolimus once daily, or immediate release tacrolimus twice daily

after transplantation. The dose and time after transplantation of the first tacrolimus administration, designated as Day 1, varied by organ transplanted (Table 1).

Table 1. Initial dose and day of first dose of tacrolimus based on transplanted organ

Transplanted organ	Initial dose (mg/kg)	Tacrolimus Day 1
Heart	0.075	4 days after skin closure
Liver	0.3	2 days after skin closure
Kidney	0.3	24 hours after reperfusion

Subsequent doses were adjusted based on clinical evidence of efficacy, adverse events and achievement of recommended target whole blood trough levels (days 1-21: 10- 20 ng/mL; days 22 onward: 5-15 ng/mL). Whole blood samples were collected before dosing and at a variety of time points post-dose on days 1, 7, and 28 to provide pharmacokinetic profiles.

The average whole blood concentration time curve for 24 hours after administration of prolonged release tacrolimus was smooth, whereas immediate release tacrolimus had a biphasic response. After the first dose of tacrolimus, systemic exposure (AUC) was approximately 35% lower in the group given the prolonged release group compared to those given the immediate release formulation. By day 28, once patients were at steady state after their last dose adjustment, the systemic exposure was similar for both formulations. The linear relationship between AUC and the concentration at 24 hours was also similar between the formulations. This indicates the same target trough levels will result in similar systemic exposure, and the same therapeutic drug monitoring method can be used.[4]

Based on currently available literature, it should be noted that when converting pediatric patients from twice daily to once daily formulations of tacrolimus, or starting them on a once daily regimen, daily drug monitoring is warranted until stable concentrations are achieved.

Adverse Reactions

Tacrolimus use is associated with many adverse reactions, including diabetes, nephrotoxicity, hyperglycemia, hyperkalemia, hypomagnesemia, neurotoxicity and alopecia. When compared to other agents in the same class (e.g., cyclosporine), tacrolimus is associated with higher instances of hyperglycemia and diabetes. Children are also at a higher risk of developing infections and lymphoproliferative disorders than adult transplant recipients due to the potentially longer duration of immunosuppression.[2]

A recent study reviewed factors associated with post-transplant diabetes mellitus (PTDM) in children treated with tacrolimus after renal transplantation. Patients without PTDM were matched to patients with PTDM according to age at time of transplantation, sex and follow up duration. All patients were genotyped for SNPs relevant to tacrolimus metabolism, and a pharmacogenetic risk score was constructed to evaluate the potential relationship between risk of PTDM and level of tacrolimus exposure. [10]

Of the 98 children included in the study, 18 (18%) developed PTDM in the first four years after tacrolimus initiation. Of the 18 patients who developed PTDM, 12 (67%) developed PTDM in the first year after initiation of tacrolimus. Tacrolimus dosage at the time of PTDM diagnosis was within the recommended dose range for children after renal transplantation (0.25 +/- 0.12 mg/kg/day). There was a trend between age at transplantation and occurrence of PTDM, with older children developing PTDM earlier than younger children. None of the SNPs tested were significantly associated with PTDM, but the investigators observed a tendency for patients with POR*28 and ABCB1 to have higher rates of PTDM ($p = 0.114$ and $p = 0.066$, respectively). A multivariate analysis did not find an association between the risk of PTDM and the initial dose of tacrolimus, previous cyclosporine administration, acute rejection before tacrolimus introduction, or the number of acute rejection episodes while receiving tacrolimus; however, the POR and ABCB1 gene variants were identified as risk factors of PTDM in the population of children with renal transplantation.[10]

Novel Uses for Tacrolimus

Studies have shown tacrolimus to be useful in the treatment of refractory ulcerative colitis (UC). The first case series showing the efficacy of tacrolimus for adult patients with irritable bowel disease (IBD) was in 1998. There have since been several retrospective studies showing the efficacy of tacrolimus in pediatric patients for this indication. One early study included 46 pediatric patients with corticosteroid-refractory colitis who were initiated at a tacrolimus dose of 0.1 mg/kg twice a day and titrated to trough levels of 10-15 ng/mL for induction, and 5-10 ng/mL once in remission. This study showed that 93% of patients treated with tacrolimus avoided immediate colectomy.[11]

A subsequent retrospective review evaluated 18 patients with ulcerative colitis treated with oral tacrolimus. Of the patients included in the study, nine patients were steroid-resistant and nine were steroid-dependent. Patients were started on tacrolimus 0.2 mg/kg divided BID with goal levels of 10-15 ng/mL for the first 2 weeks, followed by goals of 7-12 ng/mL for maintenance.

Seventeen patients (94%) responded to tacrolimus therapy, with an average time to response of 8.5 days. The patients with steroid-dependent UC were more likely to achieve prolonged remission, with only two of the nine (22%) requiring colectomy. All nine of the patients with steroid resistant UC ultimately proceeded to undergo colectomy.[12] It should be noted that the long-term prognosis for these patients is not promising despite initial benefit with tacrolimus. Retrospective studies in adults have shown that the relapse-free survival rate decreases with time.

Another innovative use of tacrolimus is as an ointment formulation for the treatment of atopic dermatitis (AD). Tacrolimus is passively absorbed into the skin and reduces skin inflammation and pruritus in AD, blocking T cell activation by binding to the cytosolic immunophilin receptor to form a complex that inhibits the activity of the enzyme calcineurin.[13] Protopic (tacrolimus) ointment was made available in December 2000 as both a 0.03% and 0.1% concentration.

McCollum and colleagues reviewed the safety and efficacy of tacrolimus ointment in pediatric patients with mild to severe atopic dermatitis. Although the 0.03% formulation is the only one currently indicated for use in children between the ages of 2-15 years, short-term placebo controlled trials have evaluated both strengths in pediatric patients. When compared to placebo, tacrolimus ointment offered rapid relief from the symptoms of atopic dermatitis, with the most improvement seen in the first week of treatment. Tacrolimus ointment has also been shown to be more efficacious and have a similar safety profile compared to pimecrolimus cream, as well as some topical corticosteroids, for short-term management of atopic dermatitis.[14]

Future Studies

There are currently six studies listed on clinicaltrials.gov pending results that are evaluating appropriate dose conversions among the different tacrolimus dosage forms in pediatric patients in order to develop recommendations for switching between these medications. Conversion recommendations supported by the literature would be helpful given the concern for compliance in the adolescent population, and the benefit of a simplified once daily regimen.

Summary

There are unique areas of study regarding the use of tacrolimus in pediatric patients. The pharmacokinetics are variable in this population, leading many studies to analyze the appropriateness of switching between different available dosage forms. Tacrolimus has a narrow therapeutic index, and because of concerns for safety and efficacy in this high-risk population, pharmacogenomics is a popular area of study.

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