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Immunosuppression with Tacrolimus after Solid Organ Transplantation in Children

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Tacrolimus, previously known as FK506, has replaced cyclosporine for chronic immunosuppression after transplantation at many institutions. Although not structurally related to cyclosporine, tacrolimus has a similar mechanism of action and efficacy. While the adverse effect profiles of the two drugs are also comparable, tacrolimus is better tolerated by some patients, particularly children and adolescents. In addition, tacrolimus use has been associated with fewer episodes of late graft rejection and a reduced need for concomitant steroids.[1] This issue of *Pediatric Pharmacotherapy* will review the use of tacrolimus in pediatric patients after solid organ transplantation.

Mechanism of Action

Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Although the exact mechanism by which tacrolimus produces immunosuppression remains unknown, it appears to act through inhibition of T-lymphocyte activation. Tacrolimus binds to an intracellular protein, FKBP-12, and forms a complex with calcium, calmodulin, and calcineurin. The resulting complex inhibits the phosphatase activity of calcineurin, which prevents the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT). NF-AT is believed to initiate gene transcription for the formation of lymphokines such as interleukin-2 and gamma interferon. The clinical result of inhibition of NF-AT is immunosuppression.[1-3]

In addition, tacrolimus inhibits cell degranulation and apoptosis, blocks activation of nitric oxide synthetase, and potentiates the cellular effects of steroids. Unlike cyclosporine, tacrolimus does not increase levels of transforming growth factor-beta (TGF-β), an endogenous promoter of fibrinogenesis and smooth muscle proliferation. High levels of TGF-β have been associated with an increase in episodes of chronic renal allograft rejection.[1]

Efficacy in Pediatric Transplantation

Following an initial paper on its use in children by Tzakis in 1991, tacrolimus has become a common choice for immunosuppression following liver, kidney, and heart transplantation. Graft and patient survival rates with tacrolimus in children are similar to values reported with cyclosporine. Steroid requirements are typically lower with tacrolimus, which may lessen the growth retardation seen in transplanted children.[1]

In August 2000, Jain and colleagues from the University of Pittsburgh published a retrospective review of 233 consecutive pediatric liver transplant patients treated with tacrolimus from 1989 to 1994.[4] They compared these results to 120 children given cyclosporine during 1988 and 1989. At 9 years follow-up, the tacrolimus patients had significantly better actuarial survival rates (patient survival 85.4% versus 63.8% for cyclosporine and graft survival 78.9% versus 60.8%). There were significantly fewer episodes of rejection in the tacrolimus group (0.97 per patient versus 1.5 per patient for cyclosporine). In addition, the tacrolimus-treated patients had a lower mean steroid dose, and more were steroid-free (80% versus 32%).

The same year, the authors reported their results in 73 pediatric liver transplant recipients converted from cyclosporine to tacrolimus after a period of rejection.[5] The patient survival rate was 78.1% at 5 years and 74.6% at 8 years. Approximately 75% of the children were steroid-free after conversion to tacrolimus, which resulted in an improvement in growth.

In 2002, Trompeter and colleagues conducted a multicenter, randomized, prospective, open-label study of tacrolimus and cyclosporine as initial therapy after pediatric kidney transplantation.[6] A total 196 children completed the 6-month

study with an open extension phase. The mean tacrolimus dose decreased over time from 0.30±0.09 mg/kg/day during the first week to 0.21±0.11 mg/kg/day at 6 months. Patient survival was similar in both groups, with 97.0% in the tacrolimus group and 96.8% in the cyclosporine group. Graft survival at 6 months was 92.2% for tacrolimus and 86.0% for cyclosporine. Fewer patients in the tacrolimus group experienced rejection (36.9% versus 59.1%), and there were fewer cases of steroid-resistant rejection (7.8% versus 25.8%).

The efficacy of tacrolimus after heart, lung, and heart-lung transplantation in children (with 90, 70, and 50% 1-year survival, respectively) has been equivalent to that of cyclosporine. As with studies of liver and kidney transplants, the need for concomitant steroids has been significantly reduced with tacrolimus in these patients.[1]

Pharmacokinetics

The pharmacokinetic profile of tacrolimus has been extensively studied in children and adults. Bioavailability after oral administration is low, averaging 17 to 22%. Administration with food decreases the rate and extent of tacrolimus absorption, with the greatest effect occurring with a high-fat meal. Peak whole blood concentrations typically are achieved within 1.5 to 3 hours after an oral dose.[2,3]

Tacrolimus is highly bound to both albumin and α_1-acid glycoprotein. It also binds to erythrocytes and lymphocytes. The volume of distribution in adults is 1.4 to 1.9 L/kg, compared to an average of 2.6 L/kg after intravenous (IV) dosing in children. Tacrolimus is metabolized by cytochrome P450 3A enzymes (CYP3A4 and 5) in the liver and gut lining and serves as a substrate for P-glycoprotein. At least 15 active and inactive metabolites are produced. Tacrolimus metabolites are eliminated in the bile, with an average rate of clearance of 0.04 to 0.08 L/kg/hr in adults. Children appear to have a more rapid clearance, with an average value of 0.14 L/kg/hr. Terminal elimination half-life is highly variable, ranging from 11 to 35 hours in children and adults. Tacrolimus elimination is not affected by renal or mild hepatic dysfunction. In patients with severe hepatic dysfunction or hepatitis C, clearance is prolonged.[1-3,7,8]

Several recent studies have provided additional information on pediatric tacrolimus pharmacokinetics. In 2001, Shishido and colleagues evaluated 32 children (ages 3-15 years) after kidney transplantation.[9] In the 22 patients who received IV tacrolimus, a dose of 0.078±0.018 mg/kg/day produced a mean whole blood concentration of 27.1±6.8 ng/ml with a clearance of 2.1±0.6 ml/min/kg and a terminal half-life of 11.0±2.5 hours. With oral administration in all 32 children, an average dose of 0.60±0.16 mg/kg/day was required to maintain trough concentrations within the desired 10-20 ng/ml range (actual mean achieved 13.5±2.8 ng/ml). Bioavailability was low in this sample, with an average of 10.0±5.2% and a range of 5.1 to 26.6%. A significant correlation was observed between age and dose/trough concentration. In agreement with earlier pediatric studies, the authors noted that patients less than 5 years of age required two to three times the adult tacrolimus dose per kg, as a result of their more rapid clearance.

In addition to age-related changes, there may be pharmacokinetic differences related to the type of transplant. In 2001, Staatz and colleagues published a study of 35 children (ages 0.5-16.6 years) receiving oral tacrolimus.[10] Using nonlinear, mixed-effects modeling to determine population parameters from routine blood sampling, the authors found that tacrolimus clearance was 7-fold greater in the 8 children with whole pediatric liver transplants than in the 27 with cut-down adult liver transplants. The authors suggested that the transplanted organ may retain its age-related metabolic function.

Even after accounting for age and type of transplant, there is considerable variation in tacrolimus concentrations using standard doses. These differences may, in part, be the result of pharmacogenomic heterogeneity. It has recently been shown that black patients may require higher doses than whites or Asians because of polymorphism in the CYP3AP1 pseudogene producing a change in CYP3A5 activity.[7]

Adverse Effects

The most common adverse effects associated with tacrolimus include: tremor (48-56% from pooled data), headache (37-64%), insomnia (32-64%), hypertension (38-50%), nausea and/or abdominal pain (32-59%), diarrhea (37-44%), constipation (23-35%), hyperkalemia (13-45%), hypomagnesemia (16-48%), asthenia (11-52%), atelectasis and pleural effusion (5-36%), and rash and/or pruritus (15-36%). In addition, hyperglycemia occurs in 33 to 47% of patients receiving tacrolimus. Insulin-dependent diabetes occurs in approximately 11 to 20% of patients post-transplant. The median time to onset in one study of adult liver transplant patients was 68 days. Insulin dependence was reversible in 15% of kidney transplants and 31 to 45% of liver transplants after one year. The development of

hyperglycemia and diabetes with tacrolimus appears to be more common in blacks, in patients receiving high-dose steroids, and in patients with elevated tacrolimus concentrations.[2,3]
Children may be at greater risk from this adverse effect, as symptoms of hyperglycemia may be more difficult to recognize and delay diagnosis. Diabetic ketoacidosis requiring hospitalization was recently reported in a 14-year-old girl after one year of tacrolimus post-transplantation.[11]

Nephrotoxicity has been reported in up to 52% of kidney transplantation patients and 40% of liver transplantation patients taking tacrolimus. Renal dysfunction is typically seen early in therapy, with an increase in serum creatinine and decrease in urine output. Dosage adjustment is often adequate to reverse this effect, but some patients may require discontinuation of therapy.[2,3]

Tacrolimus-induced neurotoxicity may be manifest in a wide range of symptoms, from tremor and headache in up to 50% of patients to more severe symptoms including seizures, coma, and delirium. Neurotoxicity appears more commonly in patients with elevated tacrolimus concentrations or hepatic dysfunction leading to impaired metabolism.[2,3] It has recently been suggested that some patients may possess a genetic predisposition to tacrolimus neurotoxicity.[12] Mutation of the ABCB1 gene may cause an alteration of P-glycoprotein function, decreasing its ability to restrict distribution of tacrolimus into the brain.

Although rare, severe myocardial hypertrophy has been reported in infants, children, and adults receiving tacrolimus. Hypertrophy is seen on echocardiography as an increase in left ventricular posterior wall and intraventricular septum thickness. These changes are often associated with elevated tacrolimus concentrations and typically reverse after dose reduction or discontinuation of therapy. A recent study has suggested that this adverse effect may be more common than previously thought and occurs with both tacrolimus and cyclosporine.[13]

An increased risk of malignancy is a known complication of long-term immunosuppressive therapy. Lymphomas, carcinomas of the skin, and lymphoproliferative disease associated with Epstein-Barr virus infections have been reported in patients taking tacrolimus, and may be more common in children than adults. In a retrospective evaluation of 326 pediatric liver transplant patients from the University of Pittsburgh, two of the 47 patients who died had post-transplant lymphoproliferative disease.[14]

Rare hypersensitivity reactions, including anaphylaxis, have been reported with IV tacrolimus. The castor oil derivative used in this formulation is believed to be the cause.[2,3]
While the overall tolerability of tacrolimus and cyclosporine is similar, there are differences which may guide drug selection. In comparison with cyclosporine, the incidence of headache, insomnia, tremor, diarrhea, nephrotoxicity, and hyperglycemia appear to be greater with tacrolimus. Conversely, cyclosporine has been more frequently associated with hirsutism, gingival hyperplasia, constipation, hypertension, and dyslipidemias.[1]

Drug Interactions

The metabolism of tacrolimus by CYP3A and P-glycoprotein makes it prone to drug interactions (Tables 1 and 2).[2,3,15] In many cases, the interaction does not preclude use of the drug, as long as the dose of tacrolimus is adjusted to maintain the desired whole blood concentrations and the patient is followed for adverse effects.

Table 1. Substances that may increase tacrolimus concentrations

Antifungal agents		
Clotrimazole	Fluconazole	Itraconazole
Ketoconazole	Miconazole	
Calcium channel blockers		
Diltiazem	Nicardipine	Nifedipine
Verapamil		
Corticosteroids		
Dexamethasone	Methylprednisolone	
Gastrointestinal prokinetic agents		
Cisapride	Metoclopramide	
Macrolide antibiotics		
Clarithromycin	Erythromycin	Troleandomycin
Other substances		
Bromocriptine	Chloramphenicol	Cimetidine
Cyclosporine	Danazol	Ethinyl estradiol
Grapefruit juice	Metronidazole	Nefazodone
Omeprazole	Protease inhibitors	Theophylline

Table 2. Substances that may decrease tacrolimus concentrations

Antibiotics		
Rifabutin	Rifampin	
Anticonvulsants		
Carbamazepine	Phenobarbital	Phenytoin
Other substances		
Antacids	St. John's wort	

Concomitant use of other nephrotoxins (eg, aminoglycosides, amphotericin, cisplatin, or nonsteroidal anti-inflammatory agents) should be carefully considered in patients receiving tacrolimus. Because of the additive risk for infection and nephrotoxicity, tacrolimus should not be given simultaneously with cyclosporine. In patients converting to tacrolimus,

cyclosporine should be discontinued at least 24 hours prior to starting tacrolimus.[2,3]

Immunosuppression may reduce the efficacy of live vaccines (eg, measles, mumps, rubella, varicella). The risk:benefit ratio should be evaluated for each pediatric transplant patient.

Tacrolimus may reduce the clearance of mycophenolate mofetil, increasing the risk of toxicity from this agent. The two medications are often given simultaneously without adverse effects, but patients starting therapy with this combination should be closely monitored.

Dosing Recommendations

Initial dosing recommendations for tacrolimus in children and adults are 0.03 to 0.1 mg/kg/day IV as a continuous infusion or 0.15 to 0.3 mg/kg/day orally, divided and given every 12 hours. As noted previously, younger children may require a two to three times higher dose per kg than adults. Doses should be adjusted to maintain trough tacrolimus concentrations of 5 to 20 ng/ml using the whole blood ELISA assay.

Parents of children receiving tacrolimus should be aware of the need to give it on a regular schedule. Although food reduces the bioavailability of tacrolimus, administration with meals may be necessary to counteract nausea. Tacrolimus should not be administered with grapefruit juice or antacids.[1-3]

Availability

Tacrolimus (Prograf®; Fujisawa) is available as 0.5, 1, and 5 mg capsules and a 5 mg/ml injection in 1 ml ampules.[2] An extemporaneous formulation has been developed to make a 0.5 mg/ml suspension for patients who are unable to swallow capsules or require small doses.[11]

Summary

Tacrolimus offers an alterative to cyclosporine for immunosuppression after solid organ transplantation in children. Although not without significant adverse effects, tacrolimus may provide greater protection from rejection and lessen the need for steroids. In addition, use of tacrolimus may avoid adverse effects associated with reduced cyclosporine compliance, such as gingival hyperplasia and hirsutism.

References

1. Spencer CM, Goa KL, Gillis JC. Tacrolimus: an update of its pharmacology and clinical efficacy in the management of organ transplantation. Drugs 1997;54:925-75.
2. Prograf® product information. Fujisawa. May 2002. Available at www.fujisawa.com/medinfo/pi/pi_page_pg.htm
3. Tacrolimus. In: Burnham TH, ed. Drug Facts and Comparisons. 2003. St. Louis: Facts and Comparisons, Inc.:1568c-1570a.
4. Jain A, Mazariegos G, Kashyap R, et al. Comparative long-term evaluation of tacrolimus and cyclosporine in pediatric liver transplantation. Transplantation 2000;70:617-25.
5. Reyes J, Jain A, Mazariegos G, et al. Long-term results after conversion from cyclosporine to tacrolimus in pediatric liver transplantation for acute and chronic rejection. Transplantation 2000;69:2573-80.
6. Trompeter R, Filler G, Webb NJA, et al. Randomized trial of tacrolimus versus cyclosporin microemulsion in renal transplantation. Pediatr Nephrol 2002;17:141-9.
7. Macphee IAM, Fridericks S, Tai T, et al. Tacrolimus pharmacogenetics: polymorphisms associated with expression of cytochrome P4503A5 and p-glycoprotein correlate with dose requirement. Transplantation 2002;74:1486-9.
8. Wallemacq PE, Verbeeck RK. Comparative clinical pharmacokinetics of tacrolimus in paediatric and adult patients. Clin Pharmacokinet 2001;49:283-95.
9. Shishido S, Asanuma H, Tajima E, et al. Pharmacokinetics of tacrolimus in pediatric renal transplant patients. Transplant Proc 2001;33:1066-8.
10. Staatz CE, Taylor PJ, Lynch SV, et al. Population pharmacokinetics of tacrolimus in children who receive cut-down or full liver transplants. Transplantation 2001;72:1056-61.
11. Keshavarz R, Mousavi M, Hassani C. Diabetic ketoacidosis in a child on FK506 immunosuppression after a liver transplant. Pediatr Emerg Care 2002;18:22-4.
12. Yamauchi A, Ieiri I, Kataoka Y, et al. Neurotoxicity induced by tacrolimus after liver transplantation: relation to genetic polymorphisms of the ABCB1 (MDR1) gene. Transplantation 2002; 74:571-3.
13. Roberts CA, Stern DL, Radio SJ. Asymmetric cardiac hypertrophy at autopsy in patients who received FK506 (tacrolimus) or cyclosporine A after liver transplant. Transplantation 2002;74:817-21.
14. Fridell JA, Jain A, Reyes J, et al. Causes of mortality beyond 1 year after primary pediatric liver transplant under tacrolimus. Transplantation 2002;74:1721-4.
15. Christians U, Jacobsen W, Benet LZ, et al. Mechanisms of clinically relevant drug interactions associated with tacrolimus. Clin Pharmacokinet 2002;41:813-51.
16. Jacobson PA, Hohnson CE, West NJ, et al. Stability of tacrolimus in an extemporaneously compounded oral liquid. Am J Health-Syst Pharm 1997;54:178-80.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 4/25/03:

1. Sarapin (Sarapin®) was added to the Formulary for the treatment neuralgic pain. This product is a sterile solution of compounds from the pitcher plant which act as a neurolytic. Prescribing is restricted to Pain Management.
2. Temozolomide (Temodar®) was added for the treatment of refractory anaplastic astrocytoma.
3. Alemtuzumab (Campath®) was added for the treatment of B-cell chronic lymphocytic leukemia.
4. Granisetron (Kytril®), a selective 5-HT_3 receptor antagonist antiemetic, was added for a 3-month trial period in the perioperative setting.

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