

Tacrolimus: review of pharmacokinetics, pharmacodynamics, and pharmacogenetics to facilitate practitioners' understanding and offer strategies for educating patients and promoting adherence

Kidney transplantation requires lifelong immunosuppression with agents that prevent allograft rejection. Immunosuppressive regimens typically include a steroid, an immune modulator (eg, azathioprine, mycophenolate mofetil, or mycophenolate sodium), and a calcineurin inhibitor, either cyclosporine or tacrolimus. Tacrolimus is metabolized by cytochrome P450 3A4 in both the liver and small intestine. Drugs that are substrates of cytochrome P450 3A4, as well as inhibitors and inducers of cytochrome P450 3A4, can cause significant interactions with tacrolimus. A review of the pharmacodynamics and pharmacokinetics of tacrolimus is important to enhance practitioners' understanding when using tacrolimus after kidney transplantation. It is also important to educate patients and their families about tacrolimus. Patients' adherence to this medication regimen is pivotal for allograft survival. A consistent and comprehensive approach to education and discharge teaching is a key component of adherence and the attainment of therapeutic drug levels. At Shands Jacksonville Transplant Center, discharge education and teaching tools aid the transplant professionals and facilitate patients' adherence. This in turn supports the goals of maintaining therapeutic serum levels of tacrolimus and improving renal allograft survival. (*Progress in Transplantation*. 2009;19:277-284)

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Tacrolimus is indicated for the prevention of organ rejection in patients receiving a liver, kidney, or heart transplant and improves solid organ survival.¹ Because of the complex pharmacodynamics, pharmacokinetics, and pharmacogenetics of this drug, the potential exists for adverse reactions and a high incidence of drug interactions. Both practitioners and patients require extensive knowledge and training in order to optimize safe delivery of tacrolimus.^{1,2}

Shands Jacksonville Medical Center is a 695-bed urban teaching facility affiliated with the University of Florida. Our program uses a comprehensive patient education and discharge process for the kidney transplant recipients and their families. This process is designed

to facilitate immunosuppression adherence in our kidney transplant recipients.

Tacrolimus Pharmacodynamics

Tacrolimus is widely used to prevent acute rejection after solid-organ transplantation.¹ Tacrolimus is a macrolide antibiotic produced by the soil fungus *Streptomyces tsukubaensis* and suppresses both humoral and cell-mediated immune responses by inhibiting calcineurin.³ Calcineurin is a protein phosphatase known as protein phosphatase 2B. It is responsible for activating the transcription of interleukin 2 (IL-2), which stimulates the growth and differentiation of a T-cell response. Calcineurin dephosphorylates a nuclear

factor of the activated T cell, and cytoplasmic component transcription factor can then migrate into the nucleus and activate genes involved in IL-2 synthesis. IL-2 is a powerful inflammatory catalyst implicated in allograft rejection.⁴

The allograft rejection process begins when an alloantigen is presented to the T-cell receptor and an increase in the cytoplasmic levels of calcium results. This response activates calcineurin by binding regulatory subunits and calmodulin complexes. Calcineurin induces different transcription factors that are important in the IL-2 genes. IL-2 activates helper T lymphocytes and induces the production of other cytokines. In this way, calcineurin governs the process of rejection.⁴ The amount of IL-2 produced by the helper T cells is believed to significantly influence the extent of the immune response.^{5,6}

Tacrolimus has a greater effect on the T lymphocyte than does an earlier released calcineurin inhibitor, cyclosporine.⁷ In a response to antigenic stimulation, in vitro studies on cultured CD4 helper T lymphocytes have demonstrated that tacrolimus is superior to cyclosporine in selectively inhibiting the secretion of various cytokines, including IL-2 and IL-3.^{5,8} This

difference may contribute to the greater effect of tacrolimus than cyclosporine on impairing the expression of alloantigen-stimulated T cells in solid organ transplantation.^{9,10}

The principal functions of the immune system are to defend against infections and to discriminate between self antigens and non-self antigens. The genes that determine the rejection or acceptance of tissue grafts are present in a locus on chromosome number 6 called the major histocompatibility complex. The central event in the initiation of an alloresponse is the recognition of the peptide in the major histocompatibility complex by the T-cell receptor.⁴ Tacrolimus inhibits calcineurin, thus preventing T-lymphocyte activity in response to exposure to the peptide from the major histocompatibility complex.⁵ Tacrolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits the proliferation of calcineurin.⁸ Figure 1 illustrates the area in the T cell where tacrolimus inhibits calcineurin in the immune complex reaction. Tacrolimus inhibits the T-cell cycle of nuclear translocation and IL-2 production, preventing the lymphocyte from eliciting an immune response to the peptide from the major histocompatibility complex.

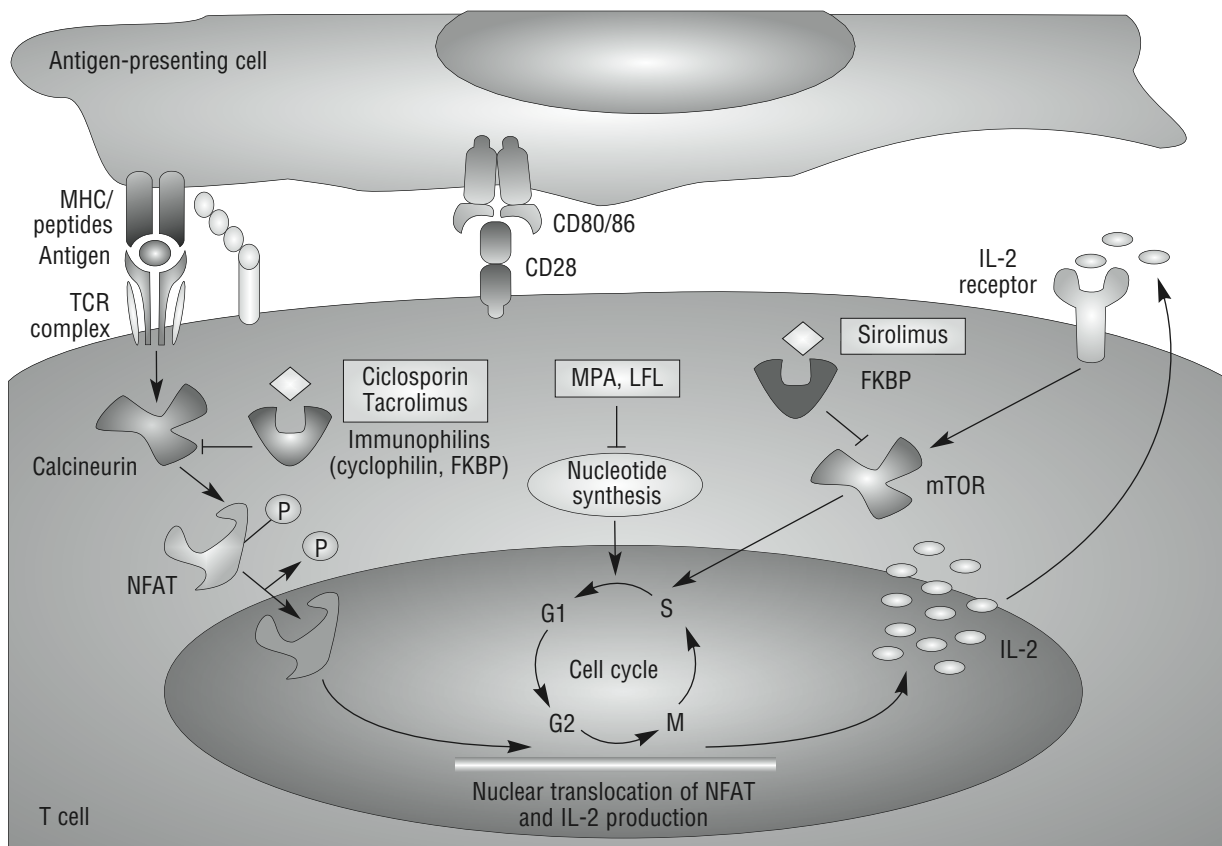


Figure 1 T lymphocyte with calcineurin inhibitor action.

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Abbreviations: FKBP, FK506-binding protein; IL, interleukin; MHC, major histocompatibility complex; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; TCR, T-cell receptor.

Tacrolimus Pharmacokinetics

The pharmacokinetic parameters of tacrolimus are quite variable among individuals. Although rapidly absorbed in the gastrointestinal tract, tacrolimus has poor oral bioavailability, ranging from 5% to 93% (mean, 25%). Peak concentrations in whole blood occur at 1 to 2 hours after oral administration, and absorption is decreased in the presence of food. After intestinal absorption, tacrolimus is primarily distributed to erythrocytes and is approximately 99% protein bound to both α -acid glycoprotein and albumin. Distribution into most tissues is extensive, and the drug also passes through the placenta and into breast milk.¹

Presystemic metabolism by cytochrome P450 (CYP)3A4 isoenzymes and P-glycoprotein occurs in the intestinal mucosa. P-glycoprotein lowers the intracellular levels of tacrolimus by pumping drug back into the intestinal lumen for further metabolism by CYP3A4. Thereafter, CYP3A4 (and to a lesser extent CYP3A5) isoenzymes in the liver provide extensive metabolism. There are at least 15 metabolites, the major metabolite being 13-O-demethyl-tacrolimus.¹¹

The terminal half-life of tacrolimus in kidney transplant recipients is approximately 8.7 hours.¹² Biliary excretion and fecal elimination are responsible for the major clearance of metabolites, whereas renal excretion plays only a small role.^{1,11}

Drug Interactions

Because tacrolimus is metabolized extensively by CYP3A4 isoenzymes and P-glycoprotein, drugs that are either inhibitors or inducers of this system may increase or decrease serum concentrations of tacrolimus. CYP3A4 inhibitors that increase whole-blood concentrations of tacrolimus include antifungal agents (fluconazole, voriconazole, ketoconazole, itraconazole, and clotrimazole), calcium channel blockers (diltiazem, nifedipine, nicardipine, and verapamil), macrolide antibiotics (erythromycin, clarithromycin, and troleandomycin), prokinetic drugs (metoclopramide and cisapride), protease inhibitors (indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, and atazanavir), and grapefruit juice. CYP3A4 inducers that are known to decrease tacrolimus concentrations include anticonvulsants (carbamazepine, phenytoin, and phenobarbital); rifamycins (rifampin and rifabutin), and St John's wort^{12,13} (Table 1).

Toxicity

There are several principal adverse effects associated with tacrolimus. Nephrotoxic effects can occur in up to 52% of patients and limit the use of the drug. However, nephrotoxic effects may be difficult to distinguish from other causes of renal failure in kidney transplant recipients. Neurotoxic effects may be manifested by tremors (15%-56%), headache (37%-64%),

Table 1 Cytochrome P450 3A4 inhibitors and inducers^a

Inhibitors (increase tacrolimus levels)	Inducers (decrease tacrolimus levels)
Amiodarone	Barbiturates
Amprenavir	Bosentan
Aprepitant	Carbamazepine
Atazanavir	Efavirenz
Cimetidine	Felbamate
Ciprofloxacin	Glucocorticoids
Clarithromycin	Modafinil
Delavirdine	Nafcillin
Diltiazem	Nevirapine
Doxycycline	Oxcarbazepine
Echinacea	Phenytoin
Enoxacin	Primidone
Erythromycin	Rifampin
Fluconazole	St John's wort
Fluvoxamine	Pioglitazone
Grapefruit juice	Topiramate
Indinavir	
Itraconazole	
Ketoconazole	
Miconazole	
Nefazodone	
Nelfinavir	
Ritonavir	
Saquinavir	
Star fruit	
Telithromycin	
Verapamil	
Voriconazole	

^a Based on data from Health and DNA Web site.¹⁴

insomnia (32%-64%), and paresthesias (17%-40%). Hypertension (38%-89%) is common, as is drug-induced diabetes (24%), exacerbated by the use of corticosteroids. Gastrointestinal disturbances reported are diarrhea (37%-72%), nausea (32%-46%), constipation (23%-35%), and anorexia (34%). Malignant neoplasms such as lymphoma and lymphoproliferative disease occur rarely (1.5%). Finally, the risk of bacterial, viral and fungal infections is increased (up to 45%), because of the immunosuppressive effect of tacrolimus^{11,15} (Table 2).

Dosage and Administration

Tacrolimus is used for primary immunosuppression after kidney transplantation, along with an immune modulator (mycophenolate mofetil/sodium or azathioprine) plus or minus a corticosteroid. It should be given orally whenever possible, although an intravenous formulation is available. Use of intravenous tacrolimus should be minimal, as it has been reported to cause anaphylaxis. The first dose of oral tacrolimus is given within 24 hours of kidney transplantation.¹ The initial dose is 0.1 mg/kg every 12 hours.¹² The dosage can be reduced during maintenance therapy, depending on clinical assessments of rejection and tolerability for each patient.¹

Table 2 Adverse reactions to tacrolimus^a

System	Adverse reaction	Frequency, %
Cardiovascular	Hypertension	38-89
	Chest pain	19
Dermatologic	Pruritus	15-36
	Rash	10-24
Electrolytes/ metabolic	Hyperglycemia	22-70
	Hyperkalemia	8-45
	Hypokalemia	13-29
	Hypophosphatemia	49
	Hypomagnesemia	16-48
	Edema	18
	Hyperlipidemia	31
Gastrointestinal	Diarrhea	37-72
	Nausea	32-46
	Anorexia	34
	Constipation	23-35
	Vomiting	14-29
	Dyspepsia	28
	Abdominal pain	29-59
Hematologic	Anemia	5-65
	Leukocytosis	32
	Thrombocytopenia	24
	Leukopenia	48
Hepatic	Ascites	27
	Abnormal liver enzyme levels	36
Immunologic	Anaphylaxis	
	Hypersensitivity reaction	
	Lymphoproliferative disorder	
	Malignant lymphoma	
Musculoskeletal	Arthralgia	25
	Back pain	17-30
Neurologic	Headache	37-64
	Tremor	15-56
	Insomnia	32-64
	Paresthesia	17-40
	Dizziness	19
	Aesthesia	11-52
	Agitation	>3
	Confusion	>3
	Seizure	>3
	Leukoencephalopathy	>3
	Ocular and otic	Abnormal vision
Ear pain		>3
Otitis media		>3
Tinnitus		>3
Psychiatric	Anxiety	>3
	Depression	>3
	Dream disorder	>3
	Hallucinations	>3
	Psychosis	>3
	Renal	Nephrotoxic effects
Urinary tract infections		16-34
Oliguria		18-19
Respiratory	Pleural effusion	30-36
	Dyspnea	5-29
	Atelectasis	5-28
	Increased cough	18

*Continued*Table 2 *Continued*

System	Adverse reaction	Frequency, %
Infectious disease	Tuberculosis	
	Cytomegalovirus	
	Epstein Barr virus	
	Candidiasis	
	Fungemia	
	Herpes simplex and zoster	
	BK polyomavirus	
	Skin and wound infections Pneumonia	

^a Based on data from Staatz and Tett¹¹ and McEvoy et al.¹⁵

Therapeutic Drug Monitoring

Considering the variability of the pharmacokinetic properties of tacrolimus among individuals and a narrow therapeutic index, drug monitoring is necessary to ensure appropriate immunosuppression and to avoid toxic effects. Drug levels are obtained as predose (12 hours after previous dose) trough concentrations in whole blood.¹ These trough levels correlate reasonably well with area under the curve, with total area under the curve being an accurate measure of drug exposure.¹⁶ Therapeutic ranges of tacrolimus after kidney transplantation are reported as a range for various times after transplant: 0-1 month, 15-20 ug/L; 1-3 months, 10-15 ug/L; and more than 3 months, 5-12 ug/L.¹¹

Tacrolimus Pharmacogenetics

Genetic mutations in the CYP450 enzyme system have been reported. Polymorphism or genetic variations in CYP3A4 and CYP3A5 have been reported that affect tacrolimus dosing and serum concentrations in kidney transplant patients.^{2,8} Genotype testing for CYP3A4 and CYP3A5 has been developed and may be helpful in dosing of tacrolimus in kidney transplant recipients.⁸ Understanding the pharmacogenetics of tacrolimus may enable individualized therapeutic dosing, resulting in adequate immunosuppression with minimization of adverse reactions. Ultimately, individualized therapeutic dosing may result in greater allograft survival.

Patients and Adherence

Studies indicate that verbal and written medication communication to patients is crucial to the success of treatments.^{17,18} Patients often have difficulty managing their medications after they are discharged. Common issues that lead to decreased medication adherence include (1) lack of understanding of how to follow a medication regimen, (2) lack of information about the medication itself, (3) discrepancies on what other medications, both prescription and over the counter, can be taken, and (4) lack of information on potential adverse reactions that must be reported to the physician.¹⁷

In a survey of 172 general medical-surgical patients contacted 4 to 18 days after discharge, Maniaci et al¹⁸ reported that only 22% could name any of the medications they were prescribed and what these medications treated. In addition, only 11% could identify any adverse reactions that needed to be reported to the practitioner. The researchers concluded that patients' knowledge about their medications after discharge from the hospital was insufficient for successful recovery. No correlation was found between patients' knowledge about their medications and their educational level, but a significant correlation was noted between patients' knowledge and patient's age exceeding 65 years ($P = .02$).¹⁸ Similarly, Kripalani et al¹⁷ reported low percentages of adherence and knowledge about medications for inner-city patients, both medical and surgical, discharged from the hospital. Finally, nurse-directed discharge education and protocols are associated with improvements in quality of life and functional capacity at home for patients with complex medication regimens such as those used to treat congestive heart failure.¹⁹

Patients tend to pass responsibility for their recovery and knowledge of medications to the professionals. Knowledge of medications and adverse reactions after discharge is poor unless a thorough process of transferring responsibility takes place.²⁰ In addition, literacy poses a major challenge. In several studies,¹⁷⁻¹⁹ researchers reported that effective teaching involves verbal interactions combined with written information to overcome literacy issues.

At Shands Jacksonville, the discharge process for adherence and understanding of tacrolimus begins before transplantation and extends beyond the discharge date. Patients meet extensively with the transplant team before the surgery. During this time, the surgeon, transplant nephrologist, social worker, and transplant coordinator provide detailed descriptions of the transplant process and immunosuppression. Once evaluated and identified as an appropriate candidate for transplantation, the patient meets extensively with the transplant program's registered nurse, who holds national certification as a transplant coordinator.

The nurse/transplant coordinator begins the medication education process by discussing the general categories of drugs that the patient will receive after transplantation. These include (1) immunosuppressive agents, (2) anti-infective prophylaxis agents, (3) anti-hypertensive agents, (4) medications that are part of maintenance therapy for comorbid conditions such as diabetes, (5) pain relievers, and (6) agents that prevent gastric distress from the multiple medications. During the session, verbal and written information is presented to the patient regarding tacrolimus (Prograf). The drug's mechanism of action, role in graft survival, adverse reactions, and interactions with medications and foods

are described. Written information is sent home with the potential recipient and his or her family. The family or significant other is included in the teaching plan.

The options for kidney transplantation include deceased donor transplantation or living donor transplantation. The recipient of a living donor organ is brought in 1 week before the elective procedure, and medication teaching is reinforced. Recipients of deceased donor organs are the greatest challenge for medication teaching.⁴ Transplantation becomes an acute event for the patient when an appropriate deceased donor organ is identified, resulting in a sense of urgency in preparation for surgery. No opportunities are available to reinforce the original medication teaching because minimizing cold ischemic time for the donor kidney takes priority. The original education for medications may have occurred weeks, months, or years before the time of the actual transplantation.

Immediately after transplantation for both living and deceased organ recipients, the discharge education process begins. Nurses on the transplant unit, having successfully completed an internally designed transplant credentialing program, administer immunosuppressive medication. During drug delivery at the bedside, patients are provided with information on each medication's name, dose, frequency, and indication. The bedside nurse also describes any adverse reactions that may occur that should be reported. Teaching about tacrolimus is the most extensive discussion. This drug is described to the patient as the main immunosuppressive agent leading to transplant survival. Patients are reminded with each dose of medication delivered by the nurse that the absence of the drug in the body will result in rejection of the kidney.

The transplant coordinator and social worker verify approval for dispensing the patient's medications based on insurance, and the transplant coordinator obtains the medications from the outpatient pharmacy. The coordinator then prepares a 7-day supply for each patient. Before discharge, the coordinator physically places this supply in a 7-day pill dispenser. The dispenser separates medications into 4 administration times: morning, noon, evening, and bedtime. Medications are arranged in the pill dispenser according to time of delivery. Medications taken on an as-needed basis remain in a prescription bottle.

Before discharge, the transplant coordinator meets with the patient and the patient's family to discuss the medication regimen and how the medications are arranged in the pill dispenser. Medications are individualized for each patient and numbered on a standard medication discharge tool (Figure 2). In addition, each prescription bottle has the corresponding number as it appears on the medication discharge tool to aid in refilling the 7-day dispenser accurately. The pill dispenser, filled with a 7-day supply of actual medications,


MEDICATION FLOW SHEET University of Florida Transplant Center and Shands Jacksonville 				
Patient's name: Date of birth:	Date of transplant:		Allergies:	
	Medication schedule TYPE:			
MEDICATIONS	MORNING	NOON	EVENING	BEDTIME
1. Prograf 1 mg (tacrolimus) (immunosuppressant)	X capsules			X capsules
2. Myfortic 180 mg (mycophenolate sodium) (immunosuppressant)	X tablets			X tablets
3. Prednisone 5 mg (take for one week then stop)	1 tablet			
4. Valcyte 450 mg (valganciclovir) (*take on Mon/Wed/Fri) (antiviral)	1 tablet			
5. Aspirin 81 mg (enteric coated) (antiplatelet)	1 tablet			
6. Bactrim DS (sulfamethoxazole-trimethoprim) (*take on Mon/Wed/Fri) (antibiotic)	1 tablet			
7. Mycelex troche 10 mg (clotrimazole) (dissolve in mouth – do not chew) (antifungal)	1 tablet	1 tablet	1 tablet	1 tablet
8. Zantac 150 mg (ranitidine) (antacid)				1 tablet
9. Nu-Iron 150 mg (polysaccharide-iron complex) (iron supplement)	1 capsule			1 capsule
10. Surfak 240 mg (docusate calcium) (stool softener only if needed)				1 capsule
11. Demadex 20 mg (torsemide) (water pill)	X tablets			
12. Kayexalate (sodium polystyrene sulfonate) *use only if directed by transplant staff				

Figure 2 Medication flow sheet used at University of Florida Transplant Center and Shands Jacksonville.

and the prescription bottles are given to the patient and the patient's family upon discharge. The patient is instructed to use the discharge medication tool to continue reinforcement of the medication regimen and understanding of each medication. In addition, the patient and the patient's family are sent home with a teaching fact sheet for follow-up discharge instructions (Figure 3).

Once the patient is discharged, an outpatient visit within 2 to 3 days is scheduled for the outpatient transplant clinic. The patient and the patient's family meet with the transplant coordinator and surgeon in the outpatient clinic. Patients are instructed to hold and then bring the morning dose of tacrolimus to the outpatient clinic on the day of the first clinic visit. The transplant coordinator explains the rationale for therapeutic trough

measurements. Blood for tacrolimus trough levels is obtained, and the patient is given the morning dose of tacrolimus immediately after the blood sample is obtained. Patients are to bring all medications, the 7-day pill dispenser, and the discharge medication tool at this time. The medications are discussed and reinforced with the patient and the patient's family during this clinic visit. A follow-up appointment is set for 1 day before the 7-day pill dispenser is completed. If any medications change within that time frame, the transplant coordinator calls or meets with the patient to ensure appropriate understanding of the medication change.

During the second postoperative visit to the clinic, the same procedure is used to obtain blood samples to measure the trough levels of tacrolimus. The transplant


<h1 style="background-color: #cccccc; padding: 10px; display: inline-block;">You and Your New Kidney</h1> 	
<h2>University of Florida Transplant Center and Shands Jacksonville</h2>	
<p><u>Important Telephone Numbers</u></p> <p>Clinic – 244-9800 Medication Refill Line – 244-9849 After hours On-Call – 244-9800 Toll Free Number – 1-888-749-4850 Social Worker – 244-9804 Financial Coordinator – 244-9859 Hospital Main Number – 244-0411</p> <p><u>Mailing Address:</u></p> <p>580 W. 8th Street, Suite 8000 Jacksonville, FL 32209</p> <p><u>Reminders:</u></p> <ol style="list-style-type: none"> Do not take your Prograf dose prior to your labs being drawn. Call your Pharmacy before you run out of medications; don't wait until the last minute. Call the Transplant Nurse/MD for: <ul style="list-style-type: none"> *Temperature >100°F (38°C) *Breathing problems *Increased pain or tenderness at the transplant site *Burning or pain with urination *Frequent urination or decreased urine output *Ongoing vomiting or diarrhea *Chest discomfort *Bleeding Follow up with your Primary Care Physician or Nephrologists for non-transplant-related issues. If you have to be hospitalized or visit another physician, take your medication folder (list) with you so the medical staff knows what medications you are taking. Do not eat GRAPEFRUIT or GRAPEFRUIT JUICE, herbs, or dietary supplements. 	<p><u>General Instructions</u></p> <ol style="list-style-type: none"> No lifting greater than 10 lbs until 6 weeks after transplant. No lifting greater than 20 lbs until 6-12 weeks after transplant. No jogging or running on hard surfaces, such as cement, until 3 months after transplant. You may shower and blot incision dry with a clean towel, unless instructed otherwise. <p><u>Returning to Work</u> Depending on the type of work you do, we recommend you return 4-6 weeks after transplant (refer to the no-lifting restrictions above).</p> <p><u>Sexual Activity & Pregnancy</u> Your new kidney is well protected. Sexual activity will not harm your transplanted kidney. It is best to avoid strenuous sexual activity for about 4 weeks after transplant; this is to allow healing of the incision. (Remember to protect yourself at all times from the risk of sexually transmitted diseases) Women should wait at least 2 years before becoming pregnant and then prior to pregnancy you should discuss family planning with your transplant team and gynecologists.</p> <p><u>Immunizations after transplant</u> (usually given by Primary Care or Health Dept.) These are recommended 6 months after transplant if needed.</p> <p><u>Can receive the following: (YES)</u> Inactive polio vaccine Tetanus/diphtheria booster (every 10 years) T.B. skin test Influenza A & B (flu shot) Pneumovox (booster 5 years after transplant)</p> <p><u>Cannot receive the following: (NO)</u> Smallpox Measles Mumps Rubella Oral polio Chickenpox</p> <p><u>When Can I Drive?</u> 4 weeks after transplant you can resume driving. (Keep in mind, you should not be operating a vehicle under the influence of pain medication).</p> <p><u>Skin Care</u> Transplant medications put you at a higher risk of skin cancer; it is important that you use appropriate clothing when out in the sunlight and wear sunscreen with an SPF of 30 or greater for adequate protection.</p>

Figure 3 Discharge teaching sheet used at University of Florida Transplant Center and Shands Jacksonville.

coordinator facilitates and supervises the patient and the patient's family as they fill the 7-day pill dispenser with the appropriate medications. This process

repeats in subsequent weekly visits until therapeutic tacrolimus levels are sustained and patients and their families develop a pattern of proficiency.

Patients are urged to bring all medications, the 7-day pill dispenser, and the discharge medication tool to all follow-up appointments and if readmitted to the hospital. This process reinforces the teaching and facilitates learning and adherence to any alterations in the medication regimen at that time. Medication changes are made on the discharge medication sheet and to the pill box simultaneously.

The process of pretransplant, peritransplant, and posttransplant education has worked well with the patients at Shands. Those patients who do not achieve therapeutic levels by 4 weeks after the transplant surgery undergo an analysis of area under the curve for tacrolimus. This analysis identifies metabolic dynamics and bioavailability of the drug and may be further explained by genetic mutations of the CYP3A4 enzyme.⁸ These patients may require unusually high or low doses of tacrolimus to achieve therapeutic levels and are closely monitored with weekly visits until a steady state is achieved.

Conclusions

Owing to the complex pharmacology of tacrolimus, proficient practitioners require a broad understanding and patients and their families require extensive education to facilitate adherence to the immunosuppressive regimen after transplantation. Knowledgeable practitioners, active participation of patients and their families in medication adherence, verbal reinforcement, and written information on tacrolimus have been a winning combination at Shands Jacksonville.

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References

1. Scott LJ, McKeage K, Keam SJ, Plosker GL. Tacrolimus: a further update of its use in the management of organ transplantation. *Drugs*. 2003;63(12):1247-1297.
2. Utecht KN, Hiles JJ, Kolesar J. Effects of genetic polymorphisms on the pharmacokinetics of calcineurin inhibitors. *Am J Health Syst Pharm*. 2006;63(23):2340-2348.
3. Kino TK, Hatanaka H, Hashimoto M, et al. FK-506, a novel immunosuppressant isolated from a Streptomyces. *J Antibiot*. 1987;40(9):1249-1255.
4. Danovitch G. *Handbook of Kidney Transplantation*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
5. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi AB. Strategies to improve long-term outcomes after renal transplantation. *N Engl J Med*. 2002;346(8):580-590.
6. Massimo C, Fantini MC, Becker RC, Kiesslich R, Neurath MF. Drug insight: novel small molecules and drugs for immunosuppression. *Nat Clin Pract Gastroenterol Hepatol*. 2006;3(11):633-644.
7. Niwa T, Yamamoto S, Saito M, Toshifumi S, Shiraga T, Takagi A. Effect of cyclosporine and tacrolimus on cytochrome P450 activities in human liver microsomes. *Yakugaku Zasshi*. 2007;127(1):209-216.
8. Thervet E, Anglicheau D, King B, et al. Impact of cytochrome p 450 3A4-3A5 genetic polymorphism on tacrolimus doses and concentration-to-dose ratio in renal transplant recipients. *Transplantation*. 2003;76(8):1233-1235.
9. MacLeod AM, Thompson AW. FK 506: an immunosuppressant for the 1990's? *Lancet*. 1991;337(8732):25-27.
10. White DJ. FK506: the promise and the paradox. *Clin Exp Immunol*. 1991;83(1):1-3.
11. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet*. 2004;43(10):623-653.
12. Prograf [package insert]. Deerfield, IL: Astellas Pharma US; 2008.
13. van Gelder T. Drug interactions with tacrolimus. *Drug Saf*. 2002;25(10):707-712.
14. Health and DNA: Cytochrome P450 Substrates, Inducers and Inhibitors. <http://www.healthanddna.com/drugchart.html>. Accessed July 20th, 2008.
15. McEvoy GK, Snow EK, Miller J, et al, eds. *Tacrolimus Monograph*. AHFS Drug Information 2008. Bethesda, Md: American Society of Health-System Pharmacists; 2008:3786-3788.
16. Kapturczak MH, Meier-Kriesche HU, Kaplan B. Pharmacology of calcineurin antagonists. *Transplant Proc*. 2004;36(2 suppl):25S-32S.
17. Kripalani S, Henderson LE, Jacobson TA, Vaccarino V. Medication use among inner-city patients after hospital discharge: patient reported barriers and solutions. *Mayo Clin Proc*. 2008;83(5):529-535.
18. Maniaci MJ, Heckman MG, Dawson NL. Functional health literacy and understanding of medications at discharge. *Mayo Clin Proc*. 2008;83(5):554-558.
19. Kutzleb J, Reiner D. The impact of nurse-directed patient education on quality of life and functional capacity in people with heart failure. *J Am Acad Nurse Pract*. 2006;18(3):116-123.
20. Weber S. Teaching nurse practitioners how to teach patients to take responsibility. *J Am Acad Nurse Pract*. 2006;18(8):346-374.