A pharmacokinetic analysis of tacrolimus ER dosing in obese kidney transplant recipients

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1.0 INTRODUCTION

1.1 Background and Rationale

Tacrolimus exhibits significant inter- and intra-individual variability of its absorption and metabolism. Because of this variability, standard dosing is not an accurate predictor of drug exposure. In clinical use, tacrolimus whole blood trough concentrations are measured to ensure efficacy and safety. Furthermore, the relatively low bioavailability of tacrolimus is thought to be a result of the combination of poor water-solubility, pre-systemic metabolism of tacrolimus in the gastrointestinal tract and activity of the P-glycoprotein efflux pump found in the enterocytes of the GI tract. Tacrolimus is extensively metabolized by the cytochrome P-450 system (CYP3A). The plasma protein binding of tacrolimus is approximately 99%. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein. The distribution of tacrolimus between blood and plasma depends on several factors including hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration.

Pharmacodynamic studies have revealed that, depending on time following transplantation, maintaining whole blood trough levels between 5 and 20 ng/mL provides adequate protection against acute rejection and limits the occurrence of adverse events. The management of tacrolimus blood levels is complicated by variable intra- and inter-patient absorption, interaction with food and concomitant medications, and the relatively low bioavailability of tacrolimus from the Prograf formulation (17 ± 10% in adult kidney transplant patients).

Previous studies examining immunosuppressants have shown that drug levels in the immediate post-transplant period are a major determinant of subsequent acute cellular rejection. It is known that tacrolimus (TAC) < 10 ng/mL is associated with increased rates of acute cellular rejection by one month post-transplant.

There is controversy regarding the appropriate dosing weight to use for immunosuppressants (IS). Weights use range from ideal body weight (IBW) to total body weight (TBW) depending on the institution and drug being dosed. This becomes particularly important in the obese population when there are significant differences between IBW and TBW. Our institution has always used IBW for the dosing of all IS due to concerns for nephrotoxicity with initial high blood levels of tacrolimus. The concern in obese patients is that we are underdosing this population that could be at higher risk for rejection due to higher circulating concentrations of pro-inflammatory cytokines. The introduction of the novel use of a robotic transplantation procedure at our institution for this patient population has led to increasing numbers of transplant in obese recipients; therefore, we decided to re-evaluate our dosing protocol. Data from an internal study at UIC show that our use of IBW for tacrolimus dosing is not sufficient for the obese population (body mass index [BMI] ≥30). The dose used through month 3 was closer to 0.1 mg/kg/day when total body weight was utilized. However, the use of an adjusted body weight (aBW) is

common for medication dosing in obese patients. Adjusted body weight is calculated if the TBW is greater than 30% of the calculated IBW. aBW = IBW + 0.4(TBW - IBW). There is limited data available supporting the use of either IBW or aBW in dosing tacrolimus within obese patients as these patients are typically excluded from most clinical trials, particularly the pharmacokinetic trials. In addition, no literature is available comparing the two dosing weights to determine which leads to therapeutic concentrations most effectively.

Summary and Present Study

Tacrolimus extended release (Astagraf) has recently been approved by the FDA as a once a day dosing regimen. This formulation has the potential to improve compliance. Current dosing recommendation for the extended release formulation in renal transplant is 0.15 mg/kg/day administered once daily in the morning. There are no specifications on appropriate dosing in obese patients or on whether to use actual, ideal or and adjusted weight. It will be advantageous to understand the pharmacokinetics of this medication in the obese to determine the appropriate dosing regimen. In this study, obese patients will be randomized to receive tacrolimus extended release 0.15 mg/kg/day based on either ideal body weight (IBW) or adjusted body weight (aBW).

1.2 Description of tacrolimus extended release

ASTAGRAF XL is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction

Risks and Medication Interaction:

This study poses no additional risks to the patient. Tacrolimus is a mainstay of immunosuppressant therapy at this healthcare organization. Safety data that is collected during the usual standard of care visits will also be assessed in this study including: serum creatinine, graft function, and side effects. Additionally trough tacrolimus levels will be reviewed by study coordinator and dosage adjustments will be made as necessary to stay within goal target range. The safety data will be analyzed as descriptive data with reports of adverse effects in each study arm.

Since tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations. Dose adjustments may be needed along with frequent monitoring of tacrolimus whole blood trough concentrations when ASTAGRAF XL is administered with CYP3A inhibitors or inducers. In addition, patients should be monitored for adverse reactions including changes in renal function and QT prolongation.

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Mycophenolic Acid Products

With a given dose of mycophenolic acid (MPA) products, exposure to MPA is higher with ASTAGRAF XL coadministration than with cyclosporine coadministration because cyclosporine interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Clinicians should monitor for MPA associated adverse events and reduce the dose of concomitantly administered mycophenolic acid products, if needed.

Grapefruit Juice
Grapefruit juice inhibits CYP3A-enzymes resulting in increased tacrolimus whole blood trough concentrations, and patients should avoid eating grapefruit or drinking grapefruit juice in combination with ASTAGRAF XL.

Alcohol
Consumption of alcohol with ASTAGRAF XL may increase the rate of release of tacrolimus and/or adversely alter the pharmacokinetic properties and the effectiveness and safety of ASTAGRAF XL. Therefore, alcoholic beverages should not be consumed with ASTAGRAF XL.

Protease Inhibitors
Most protease inhibitors inhibit CYP3A enzymes and may increase tacrolimus whole blood concentrations. It is recommended to avoid concomitant use of tacrolimus with nelfinavir unless the benefits outweigh the risks. Whole blood concentrations of tacrolimus are markedly increased when coadministered with telaprevir or with boceprevir. Monitoring of tacrolimus whole blood concentrations and tacrolimus-associated adverse reactions, and appropriate adjustments in the dosing regimen of tacrolimus are recommended when tacrolimus and protease inhibitors (e.g., ritonavir, telaprevir, boceprevir) are used concomitantly.

Antifungal Agents
Frequent monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when concomitant use of the following antifungal drugs with tacrolimus is initiated or discontinued. Azoles: Voriconazole, posaconazole, itraconazole, ketoconazole, fluconazole and clotrimazole inhibit CYP3A metabolism of tacrolimus and increase tacrolimus whole blood concentrations. When initiating therapy with voriconazole or posaconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be initially reduced to one-third of the original dose and the subsequent tacrolimus doses be adjusted based on the tacrolimus whole blood concentrations. Caspofungin is an inducer of CYP3A and decreases whole blood concentrations of tacrolimus.

Calcium Channel Blockers
Verapamil, diltiazem, nifedipine, and nicardipine inhibit CYP3A metabolism of tacrolimus and may increase tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these calcium channel blocking drugs and tacrolimus are used

concomitantly.

Antibacterials
Erythromycin, clarithromycin, troleandomycin and chloramphenicol inhibit CYP3A metabolism of tacrolimus and may increase tacrolimus whole blood concentrations. Monitoring of blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly.

Antimycobacterials
Rifampin and rifabutin are inducers of CYP3A enzymes and may decrease tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these antimycobacterial drugs and tacrolimus are used concomitantly.

Anticonvulsants
Phenytoin, carbamazepine and phenobarbital induce CYP3A enzymes and may decrease tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly. Concomitant administration of phenytoin with tacrolimus may also increase phenytoin plasma concentrations. Thus, frequent monitoring of phenytoin plasma concentrations and adjusting the phenytoin dose as needed are recommended when tacrolimus and phenytoin are administered concomitantly.

St. John's Wort (Hypericum perforatum)
St. John's Wort induces CYP3A enzymes and may decrease tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when St. John's Wort and tacrolimus are coadministered.

Gastric Acid Suppressors/Neutralizers
Lansoprazole and omeprazole, the proton pump inhibitors (PPIs), as CYP2C19 and CYP3A4 substrates, share the same CYP3A4 system with tacrolimus for their hepatic elimination, and may potentially competitively inhibit the CYP3A4 metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers in which the PPIs metabolic pathway shifts from 2C19 to 3A4, as compared to those patients who are efficient CYP2C19 metabolizers. Cimetidine, a CYP2C19 and CYP3A4 inhibitor, may also inhibit the CYP3A4 metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations. Coadministration with magnesium and aluminum hydroxide antacids increase tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly.

Other Drugs
Amiodarone, bromocriptine, nefazodone, metoclopramide, danazol, ethinyl estradiol and methylprednisolone may inhibit CYP3A metabolism of tacrolimus and increase tacrolimus whole blood concentrations. Monitoring of blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are coadministered.

Dosage and Administration
The initial dose of tacrolimus extended release will be tacrolimus extended release 0.15 mg/kg/day given in the morning based on either IBW or aBW depending on which arm the patient is randomized. Subsequent doses will be adjusted to maintain the target whole blood trough level of 8-12 ng/mL per institution transplant protocols.

ASTAGRAF XL is a once daily extended-release oral formulation of tacrolimus. To ensure consistent and maximum possible drug exposure, ASTAGRAF XL capsules should be taken consistently every morning, preferably on an empty stomach at least 1 hour before a meal or at least 2 hours after a meal. ASTAGRAF XL should be swallowed whole and should not be chewed, divided, or crushed. Patients should not eat grapefruit or drink grapefruit juice in combination with ASTAGRAF XL. If a dose of ASTAGRAF XL is missed, the dose may be taken up to 14 hours after the scheduled time. Beyond the 14-hour time frame, the patient should wait until the usual scheduled time the following morning to take the next regular daily dose. It is not recommended to double the dose of ASTAGRAF XL to make up for the missed dose.

Supply and Storage
ASTAGRAF XL is supplied in short, square bottles as well as in blister cartons; the statement 'ONCE DAILY' appears on its label. ASTAGRAF XL and tacrolimus immediate-release capsules are further differentiated by different color schemes.

Store and Dispense
Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

1.3 Chemistry, Manufacturing and Control Information/Pharmacology Toxicology Information

We believe our application may rely on the previous FDA's acceptance of the CMC and Pharmacology and Toxicology information related to the approved marketed drug intended for this investigation.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this research is to determine the best dosing method of tacrolimus extended release for obese kidney transplant recipients.

3.0 INVESTIGATIONAL PLAN

3.1 Study Design

This is a prospective, randomized, single-center, dual arm study to be conducted under an FDA exempt protocol. Our site will enroll 25 eligible patients for this study. Subjects will be followed for 14 days (+/- 3 days). We anticipate that it will take one year to enroll 25 patients.

3.2 Hypothesis

Obese patients will require a tacrolimus extended release dose that is greater than that calculated using ideal body weight.

3.3 Study Population

3.3.1 Inclusion Criteria

1. The subject is a recipient of a living donor or deceased donor kidney only transplant
2. Subject is ≥ 18 years of age
3. BMI≥30 on POD 0

3.3.2 Exclusion Criteria

1. Multi-organ transplant
2. Subjects taking tacrolimus pre-transplant (i.e. positive crossmatch transplants or re-transplants)
3. Patients undergoing simultaneous sleeve gastrectomy at the time of transplant.

3.3.3 Trial Population

This study will randomize de novo kidney transplant recipients who are at least 18 years of age and obese as evidenced by a BMI ≥ 30 on the day of transplantation POD 0. Demographics at this institution are approximately 50% African American, 35% Hispanic, and 15% Caucasian.

3.4 Study Duration

Subjects will be followed for a period of 14 days. We anticipate that it will take one year to enroll 25 patients.

3.5 Study Procedures

3.5.1 Subject Screening

Subjects will be recruited from patients undergoing kidney transplantation at the University of Illinois Health System. Medical history and pre-operative surgical visit and laboratory results will be utilized for the subject screening.

3.5.2 Baseline Evaluations

- Demographics: age, gender, and race
- Height, weight and BMI
- Blood pressure

- Results of Standard of Care Preoperative CBC
- Medical History, Physical and Laboratory Tests
- Results of Standard of Care Preoperative Urine pregnancy test (for female subjects)

3.5.3 Randomization

Patients will be randomized to receive tacrolimus extended release 0.15 mg/kg/day based on either IBW or aBW within 48 hours of transplant.

3.5.4 Follow-Up Care

3.5.4.1 Scheduled Follow Up

Post-transplantation, three pharmacokinetic (PK) assessments will be performed over a 14-day period in order to determine area under the curve (AUC).

On Study Day 1, the first PK assessment will be done on the day the patient receives the first dose of study drug. This may be on post-operative day (POD) 0-2 depending on post-operative urine output and attending surgeon preference.

Additional trough level measurements will be obtained pre-dose on days 2-5.

Study Day 7 will be defined as the second PK assessment and must occur between POD 5 – 9 and prior to discharge.

Study Day 14 will be defined as the third PK assessment and must occur between 6 – 8 days after the second PK assessment which correlates to POD 11-17.

Pharmacokinetic Assessments:
Study Day 1, 7, and 14 PK blood sampling points include: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after the dose of tacrolimus extended release. This results in a total of 33 blood samples.

3.5.5 Termination

If a subject decides to withdraw from the study and desires the sole use of standard of care immunosuppressant dosing, the subject will be withdrawn and standard of care immunosuppressant dosing will be utilized.

3.6 Interim Analysis

No interim analysis are planned.

3.7 Adverse Events

3.7.1 Adverse Event Reporting

Any adverse event will be reported to the University of Illinois at Chicago Institutional Review Board (IRB) within 15 business days by submitting a prompt report. The Chairman of the IRB will be notified via this mechanism.

(1) Subject's initials and subject number
(2) Investigator's name
(3) Protocol title and number
(4) Subject's date of birth, gender, and race
(5) Concomitant medication(s): dose, route, duration of treatment, date of last dose
(6) Information regarding the adverse event:
    (i) description
    (ii) date(s) the event began and ended
    (iii) whether the experience resulted in death or was life-threatening
    (iv) whether hospitalization was required or prolonged
    (v) any treatment(s) required
    (vi) outcome(s) of treatment(s)
    (vii) Investigator's determination of relationship to the test article(s).

All adverse events will be recorded on appropriate case report form(s). A summary of the adverse events including frequency, type, and severity will be reported.

3.7.2 Serious Adverse Event Reporting

Any adverse event will be reported to the University of Illinois at Chicago Institutional Review Board (IRB) within 5 business days by submitting a prompt report. The Chairman of the IRB will be notified via this mechanism.

(1) Subject's initials and subject number
(2) Investigator's name
(3) Protocol title and number
(4) Subject's date of birth, gender, and race
(5) Concomitant medication(s): dose, route, duration of treatment, date of last dose
(6) Information regarding the adverse event:
    (i) description
    (ii) date(s) the event began and ended
    (iii) whether the experience resulted in death or was life-threatening
    (iv) whether hospitalization was required or prolonged
    (v) any treatment(s) required
    (vi) outcome(s) of treatment(s)
    (vii) Investigator's determination of relationship to the test article(s).

All adverse events will be recorded on appropriate case report form(s). A summary of the adverse events including frequency, type, and severity will be reported.

3.7.3 Stopping Rules

The investigators will stop the study in the event that the following events occur.

(1) One subject experiences death related to tacrolimus extended release.

In the event of study termination, the investigator will notify the FDA and IRB that enrollment is stopped.

3.7.4 Risk Analysis

The study drug poses no additional risks to the patient. Tacrolimus is a mainstay of immunosuppressant therapy at this healthcare organization. Risks from the study procedures include loss of confidentiality and slight pain, bruising or infection from the blood draws. Safety data that is collected during the usual standard of care visits will also be assessed in this study including: serum creatinine, graft function, and side effects. Additionally trough tacrolimus levels will be reviewed by study coordinator and dosage adjustments will be made as necessary to stay within goal target range. The safety data will be analyzed as descriptive data with reports of adverse effects in each study arm.

3.8 Data and Statistical Analysis

3.8.1 Data and Statistical Plan

All demographic data, pharmacokinetic parameters, and laboratory data will be summarized using descriptive statistics. For continuous data, the mean, standard deviation, median, minimum and maximum will be reported and compared using a paired t-test. For categorical data, percent and frequency will be reported. For the endpoint comparing percents between aBW and IBW, Chi-square analyses with Fisher's Exact as needed will be conducted. Noncompartmental pharmacokinetic parameters (AUC0-24, Cmax, Tmax, C24, T½) will be calculated from blood concentration-time data. In addition, pharmacokinetic profiles will be analyzed using nonlinear mixed effects modeling to assess differences in rate of absorption and clearance between the aBW and IBW groups. A sample size of 10 subjects per group will be recruited for this pilot PK investigation.

3.8.2 Data Collection and Storage

We will collect relevant medical history information from the subject's medical records including illnesses and hospitalizations that occurred prior to or occur after subject participation in the research. Additionally, we will collect age, gender, race, height, weight, BMI, CBC, medical history, physical examination, laboratory tests, and urine pregnancy test (for female subjects). All data will be recorded on case report forms and used for analysis. Results will be compiled to assess aggregate outcomes and address the issues of reliability and efficacy. Data will be maintained in a database in a password protected computer.

3.8.3 Pharmacogenetic Analysis

One additional sample will be stored for potential future analysis.

3.8.4 Endpoints

1. Difference in tacrolimus exposure (AUC24) in obese patients dosed using aBW compared to IBW.
2. Difference in the time to a therapeutic tacrolimus trough level in the aBW group compared to the IBW group.

While there is limited data for dosing tacrolimus in the obese patient population internal data conducted at the University of Illinois Health System has demonstrated a statistically significant difference between dosing based on ideal body weight and actual body weight. Additionally the acute rejection rate was 55% in obese patients and 22% in non-obese patients, possibly as a result of under dosing in the obese population. It is well established that low tacrolimus levels especially in the first week of transplant are associated with acute rejections. At the same time high tacrolimus levels increase the risk of nephrotoxicity. Therefore, it is vital that the correct weight be utilized in dosing tacrolimus extended release, especially in a medication that will require a full day to wait for a dosage adjustment. The proposed endpoints will give the transplant community a better understanding of which weight to utilize in dosing this unique patient population. The AUC calculation will help to optimize the appropriate dosing in the obese patients to ensure a therapeutic level is maintained in a medication with high lipophilicity.

4.0 SUMMARY OF PREVIOUS HUMAN EXPERIENCE

We believe our application can rely on the FDA's acceptance of the previous human experience related to the approved marketed drug intended for investigation. Please refer to pages 27-30 of the package insert.

5.0 REFERENCES

Kino, T., et al. FK-506, a novel immunosuppressant isolated from a Streptomyces. II. Immunosuppressive effect of FK-506 in vitro. J. Antibiot. 40, 1256-1265 (1987).

Laskow, D.A., et al. The role of tacrolimus in adult kidney transplantation: a review. Clin. Transplant. 12, 489-503 (1998).

Shapiro, R. Tacrolimus (FK-506) in kidney transplantation. Transplant. Proc. 29, 45 47 (1997).

Ihara, H., et al. Intra- and interindividual variation in the pharmacokinetics of tacrolimus (FK506) in kidney transplant recipients--importance of trough level as a practical indicator. International journal of urology : official journal of the Japanese Urological Association 2, 151-155 (1995).

Staatz, C., Taylor, P. & Tett, S. Low tacrolimus concentrations and increased risk of early acute rejection in adult renal transplantation. Nephrol. Dial. Transplant. 16, 1905-1909 (2001).

Borobia, A.M., et al. Trough Tacrolimus Concentrations in the First Week After Kidney Transplantation Are Related to Acute Rejection. Ther. Drug Monit. 31, 436 442 (2009).

O'Seaghdha, C., et al. Higher tacrolimus trough levels on days 2-5 post-renal transplant are associated with reduced rates of acute rejection. Clin. Transplant. 23, 462-468 (2009).

Olyaei, A.J., de Mattos, A.M. & Bennett, W.M. Nephrotoxicity of immunosuppressive drugs: new insight and preventive strategies. Current opinion in critical care 7, 384-389 (2001).

Stratta, P., et al. The interactions of age, sex, body mass index, genetics, and steroid weight-based doses on tacrolimus dosing requirement after adult kidney transplantation. Eur. J. Clin. Pharmacol. 68, 671-680 (2012).

Kuypers D.R., Peeters P.C., Sennesael J.J. Improved adherence to tacrolimus once daily formulation in renal recipients: a randomized controlled trial using electronic monitoring. Transplantation 95, 333-340 (2013).

Appendix A
Table 1: Schedule of Visits & Procedures
A pharmacokinetic analysis of tacrolimus ER dosing in obese kidney transplant recipients

Schedule of Visits and Procedures	**Prior to Transplant**	**Visit 1**	**Visit 2**	**Visit 3**
Post Operative Day		**0-2**	**5-9**	**11-17**
Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Randomization	X			
Medical History	X			
Physical Exam	X			
Demographics	X			
Height	X			
Weight/BMI	X			
Basic chemistry profile	X	X	X	X
Hematology profile	X	X	X	X
Urine pregnancy test (if female, as needed)	X			
Tacrolimus level (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours post dose)		X	X	X
Concomitant medications	X	X	X	X
Adverse Event Reporting	X	X	X	X

Appendix B **Consent to Participate in Research**
Appendix C **Case Report Forms (Eligibility, Baseline Evaluation)**
Appendix D **24 Hour PK Flowsheet**
Appendix E **Package Insert for Tacrolimus Extended Release**
Appendix F **Investigator Curriculum Vitae and Medical License**