Once a Day Immunosuppression Regimen: Outcomes and Compliance

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A Introduction

A1 Study Abstract

Compliance with immunosuppression medications remains a major issue in kidney transplant recipients. Despite advanced technologies of reminders and alarms, many patients often miss doses of immunosuppression. This results in significant fluctuation in the level of immunosuppression which might increase the risk of rejection and graft loss. Azathioprine is a once a day medication that reduces purine synthesis through direct inhibition of the cell cycle. Similar kidney function and graft survival was found in long-term follow up studies comparing azathioprine to mycophenolate mofetil. In addition, unlike mammalian target of rapamycin inhibitors, azathioprine is not associated with nephrotoxicity or proteinuria. This study aims to compare a once a day regimen of immunosupressents (Envarsus and azathioprine) versus a twice a day regimen (immediate release tacrolimus and mycophenolic acid), observing patient compliance and outcome.

A2 Primary Hypothesis

We hypothesize that a once a day immunosuppressive regimen of Envarsus and Azathioprine (in addition to prednisone) will increase compliance and improve outcomes compared to a twice a day immunosuppressive regimen.

A3 Purpose of the Study Protocol

The protocol provides us the ability to separate and follow patients who are on a once daily vs twice daily regimen of immunosuppression. Patients are followed according to the usual follow-up in the clinics, and there are no additional other study visits included with the study.

B Background

B1 Prior Literature and Studies

Kidney transplant recipients require a strict regimen of immune suppression which can lead to high pill burden and lack of medication adherence (Budde et al., 2014; Vrijens & Heidbuchel, 2015). Lack of medical adherence can result in increased transplant failure and is estimated to exceed 30% in kidney transplant patients (Jamieson et al., 2016). Once a day regimens are accosiated with higher medical adherence than twice a day regimens. For example, nonvalvular Atrial Fibrillation patients, who are similarly burdened with high pill burden, exhibited a 21-26% higher likelihood of medication adherence when treated with a once a day regimen compared to a twice a day regimen (Laliberté et al., 2012).

Twice-daily Tacrolimus is a standard for most kidney transplant recipients as part of a normal immunosuppression regimen (Budde et al., 2014; Rostaing et al., 2016).

Tacrolimus is effective in preventing acute rejection after kidney transplantation (Budde et al., 2014). Recently, an extended release version of tacrolimus has been produced for once a day administration (LCP-TacroTM tablets [LCPT], Veloxis Pharmaceuticals, Hørsholm, Denmark) (Bunnapradist et al., 2013). Multiple studies have shown LCPT to have a higher bioavailability, requiring lower doses to maintain the same trough levels as a twice a day regimen (Budde et al., 2014; Bunnapradist et al., 2013; Rostaing et al., 2016). A phase three, double blind randomized trial showed the LCPT treatment group to have fewer treatment failures compared to the twice a day regimen (Rostaing et al., 2016). These results were seen in black recipients, older recipients, and females, which are populations that are particularly high risk for rejection (Rostaing et al., 2016). Adverse events and kidney function was similar between the LCPT and twice a day groups, showing caomparable efficacy for the treatment (Rostaing et al., 2016).

B2 Rationale for this Study

Although the efficacy of LCPT has been shown for use in kidney transplant patients, there is still a need for observing medication adherence with regards to the once a day treatment. This study will look at medical adherence with regards to its outcomes in kidney transplant recipients in order to better understand how a once a day regimen of tacrolimus may be beneficial to patients. Drugs work in a dose and time dependent manor and more emphasis is being put on electronic monitoring of medication adherence (Vrijens & Heidbuchel, 2015). This study may utilize Medisafe Medication Manager to accurately track adherence of the study medication.

C Study Objectives

C1 Primary Aim

Aim 1: To determine whether an immunosuppressive maintenance regimen of Envarsus/azathioprine regimen compared to a tacrolimus/ mycophenolic acid regimen is associated with better compliance and tolerability. This may be examined by a survey to the patients at 3 and 12 months. In addition, for patients with smart phone, we may examine their adherence through “Pill Manager by Medisafe” app. This app tracks missed/taken doses.

C2 Secondary Aim

Aim 2: To determine whether a an Envarsus/azathioprine regimen compared to a tacrolimus/ mycophenolic acid regimen is associated with a lower composite endpoint of biopsy proven acute rejection, graft loss, death and lost to follow up at 12 months after kidney transplantation. Biopsy will be performed if clinically indicated

C3 Rationale for the Selection of Outcome Measures

Acute Rejection:
We do not perform a protocol biopsy in our center, however, we have a low threshold to do a biopsy if there is an increased creatinine, proteinuria (urine protein/ creatinine > 1 gram), or de novo DSA with high level MFI. The decision of the biopsy will be based on

the decision of the clinician. Acute rejection can lead to failure and loss of the grafted kidney and is an important endpoint in many kidney transplant studies.

Graft Failure:
Graft failure will be defined by the return to hemodialysis, re-transplantation, or patient death. Death-censored graft failure will be defined as the return to hemodialysis or re-transplantation. Graft failure was chosen due to it's importance in patient outcome.

Adherence:
We may use "Pill Reminder by Medisafe" for recipients who havean iphone or android smart device. Installing the app will take place before discharge. Records from the smart phone will be emailed from the device at the clinic visit at months 3 and 12.

A survey may be distributed at months 3 and 12. Other surveys may also be distributed to examine any possible side effects.

Average variability in tacrolimus levels for the follow-up period preceding each of the surveys may be calculated and compared between the two groups

Pharmacies may be contacted to assess for timing between refills to ensure that patients have taken medication as scheduled.

These methods were chosen due to their simplicity and usefulness in gaining information on patient adherence.

D Investigational Agent

D1 Clinical Data to Date

Twice-daily Tacrolimus is a standard for most kidney transplant recipients as part of a normal immunosuppression regimen (Budde et al., 2014; Rostaing et al., 2016). Tacrolimus is effective in preventing acute rejection after kidney transplantation (Budde et al., 2014). Recently, an extended release version of tacrolimus has been produced for once a day administration (LCP-TacroTM tablets [LCPT], Veloxis Pharmaceuticals, Hørsholm, Denmark) (Bunnapradist et al., 2013). Multiple studies have shown LCPT to have a higher bioavailability, requiring lower doses to maintain the same trough levels as a twice a day regimen (Budde et al., 2014; Bunnapradist et al., 2013; Rostaing et al., 2016). A phase three, double blind randomized trial showed the LCPT treatment group to have fewer treatment failures compared to the twice a day regimen (Rostaing et al., 2016). These results were seen in black recipients, older recipients, and females, which are populations that are particularly high risk for rejection (Rostaing et al., 2016). Adverse events and kidney function was similar between the LCPT and twice a day groups, showing caomparable efficacy for the treatment (Rostaing et al., 2016).

D2 Dose Rationale and Risk/Benefits

Patients will be started on an antimetabolite in both arms (AZA or MPA) on post operation day 0 or 1 depending on the time they are able to take oral medication post surgery. Calcineurin inhibitors (Tac-IR or Tac-LCP) will be started on post operation day 1. Starting dose for Tac-IR is started at 0.1 mg/kg divided into BID. Starting dose for

Tac-LCP will be 0.08 mg/kg. These are starting doses per the center usual starting doses.
AZA starting dose will be between 1.5 - 2 mg/kg daily, rounded to nearest 50 mg. MPA (Myfortic) will be started 720 mg po BID and will be decreased to 360 mg BID when the Tac-IR trough level is therapeutic (according to the current goals in the center's protocol).

Immunosuppression administered at the study site will be recorded in the medical record and on a study drug diary. Immunosuppression doses administered at home will be recorded only on the study drug diary.

Tacrolimus trough target levels in both arms will be 7 to 10 ng/dL in the first month, then 5 to 7 afterward. Higher or lower tacrolimus trough level goals will be adjusted during the study due to clinical reasons such as history of rejection or infections post transplant at the discretion of the transplant nephrologists.

CBC, BMP or renal panel (including creatinine, eGFR) Tac trough levels will be checked once a week for the first four months then once every other weeks till the end of the study.

Known medication side effects: There are known common side effects to each medication. Tacrolimus has known side effects of tremors, sleep difficulty irregardless of its therapeutic range. Other side effects such as electrolyte abnormality in hyperkalemia, hypertension, and increased creatinine (if above therapeutic range) are known side effects as well. Both azathioprine and mycophenolate mofetil/mycophenolic acid have side effect of leukopenia and anemia. Azathioprine can also have elevated liver enzymes as a rarer side effect. Mycophenolate mofetil/mycophenolic acid have a known side effect of gastrointestinal upset or diarrhea.

E Study Design

E1 Overview or Design Summary

This will be an open label pilot study in which patients will be categorized into once a day regimen (Envarsus and azathioprine) or twice a day regimen (immediate release tacrolimus and mycophenolic acid) after kidney transplantation. We will enroll 50 patients in each arm after transplantation. Patients will be seen as per our usual follow up schedule untill month 12 (+/- 29 days) from the time of transplant (time from transplant: week 2-4, week 5-8, week 9-12, month 6, month 9 and month 12 all +/- 2 weeks) . Completion of the trial will be within 3 years. Outcomes can be reported/published by the end of the third year.

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

- Age ≥18 years
- kidney transplant recipient
- Thymoglubulin induction

2. b Exclusion Criteria

- Non-renal organ transplant
- Combined organ transplant
-
- Discharge to an acute-care facility after transplant

2.a Ethical Considerations

All patients will be given actual immunosuppressive medications (not placebo) in combinations that we have used in other patients at our transplant center. The only difference is one group will have medications dosed once a day and the other group will be on medications that are dosed twice a day, as per the medication administration recommendations.

2.b Subject Recruitment Plans and Consent Process

We will enroll 50 patients in each arm at the time of transplantation. Accounting for dropout of 20% from the study, we plan to possibly need to consent 120 patients total to obtain the 100 patient total number who complete the study. Subjects that meet the study inclusion criteria and without exclusion criteria will be approached in person prior to discharge from the hospital. The consenting process will be done in person by a study team member. Patients will be given the opportunity to look over the consent form and ask questions. A copy of the signed consent form will be provided to the patient once signed. Patients will be seen as part of the study untill month 12 (+/- 29 days) from the time of transplant.

2.c Randomization Method and Blinding

We will approach patients after transplantation, prior to discharge. If patients are eligible to receive either tacrolimus or Envarsus, then we will approach them for participation in the study. If the patient consents to the study, we will enroll patients until we reach 50 patients in each arm of the study. There is no randomization done. Because this is an open label study, blinding is not conducted.

2.d Risks and Benefits

Patients will all be on an immunosuppression regimen that we have used for patients we currently manage at our center. We have used both types of regimen on our patients, depending on tolerability and if there are any side effects that patients need switching to different regimens. Each regimen has been well tolerated by other patients. The major risks are with the side effects of the medications (see “11. d iii Expectedness of side effects to medications and adverse events”). It is expected that patients will adhere to the prescribed medication regimen, though some patients may not, especially to the twice daily regimen. We will attempt to mitigate this by aking patients use the pill reminder application. Patients are counselled on the importance of medication adherence for transplantation due to risk of rejection if they are not adherent. The benefits to patients include for those on the once daily regimen, less overall pill burden. Otherwise there is no additional benefit to patients.

2.e Early Withdrawal of Subjects

In the unlikely event that a patient is removed from study for unacceptable adverse event(s), such patient will be followed until resolution or stabilization of the adverse event. Participants that wish to withdraw from the study, or meet other early withdrawal material will have an End of Study/Early Termination Visit form filed. When possible or necessary, additional information about the patient (i.e. AEs, reason for withdrawal, etc.) will be gathered upon withdrawal of the study.

2.f When and How to Withdraw Subjects

Patients will be seen untill month 12 (+/- 29 days) from the time of transplant. At the end of this period, an End of Study/Early Termination Visit form will be filed. Subjects will be notified of their completion or withdrawal from the study and briefed appropriately on what final steps should be taken.

2.g Data Collection and Follow-up for Withdrawn Subjects

Once withdrawn from the study, for safety reasons, patients will be followed via their labs and regular clinic visits for 12 months post withdrawal.

E3 Study Drug

3.a Description

Twice-daily Tacrolimus is a standard for most kidney transplant recipients as part of a normal immunosuppression regimen (Budde et al., 2014; Rostaing et al., 2016). Tacrolimus is effective in preventing acute rejection after kidney transplantation (Budde et al., 2014). Recently, an extended release version of tacrolimus has been produced for once a day administration (LCP-TacroTM tablets [LCPT], Veloxis Pharmaceuticals, Hørsholm, Denmark) (Bunnapradist et al., 2013). Multiple studies have shown LCPT to have a higher bioavailability, requiring lower doses to maintain the same trough levels as a twice a day regimen (Budde et al., 2014; Bunnapradist et al., 2013; Rostaing et al., 2016).

Azathioprine is a once a day medication that reduces purine synthesis through direct inhibition of the cell cycle. Similar kidney function and graft survival was found in long-term follow up studies comparing azathioprine to mycophenolate mofetil. In addition, unlike mammalian target of rapamycin inhibitors, azathioprine is not associated with nephrotoxicity or proteinuria.

3.b Treatment Regimen

Patients will be started on antimetabolite in both arms (AZA or MPA) on post operation day 0 or 1. Calcineurin inhibitors (Tac-IR or Tac-LCP) will be started on post operation day 1. Starting dose for Tac-IR will be 0.1 mg/kg divided into BID. Starting dose for Tac-LCP will be 0.08 mg/kg.

Immunosuppression administered at the study site will be recorded in the medical record and on a study drug diary. Immunosuppression doses administered at home will be recorded only on the study drug diary.

Tacrolimus trough target levels in both arms will be 7 to 10 ng/dL in the first month, then 5 to 7 afterward.

CBC, BMP or Renal panel (including creatinine, eGFR) Tac trough levels will be checked once a week for the first four months then once every other weeks as part of standard of care labs post transplant. These will be collected as data points during the study duration.
AZA starting dose will be 2 mg/kg, rounded to nearest 50 mg. MPA (Myfortic) will be started 720 mg po BID and will be decreased to 360 mg BID when the Tac-IR trough level is therapeutic (according to the current protocol).

3.c Method for Assigning Subjects to Treatment Groups

We will approach patients after transplantation. Patients will either receive tacrolimus or Envarsus based on insurance coverage. We will approach patients for the study after we have determined the form of calcineurin inhibitor they will be taking If the patient consents to the study, we will enroll patients until we reach 50 patients in each arm of the study. If needed, the antimetabolite may be transitioned to the once or twice daily dosed medication, prior to discharge so that they may receive the medications prior to their discharge from the hospital. Because this is an open label study, blinding is not conducted.

3.d Preparation and Administration of Study Drug

Study medications may be self-administered by the patient. When not on the study site, all medications will be ordered through patient's preferred pharmacy. Suggestion will be made to utilize only subspecialty pharmacies.

3.e Subject Compliance Monitoring

We may use "Pill Reminder by Medisafe" for recipients who have I-phone or android smart device. Installing the app will take place before discharge. Records from the smart phone will be emailed from the device at the clinic visit at months 3 and 12. We understand that not all paitents may have a smart device/phone, and so we plan to also use a survey – BAASIS. The BAASIS survey may be distributed at months 3 and 12. Average variability in tacrolimus levels for the follow-up period preceding each of the surveys may be calculated and compared between the two groups. Pharmacies may be contacted to assess for timing between refills to ensure that patients have taken medication as scheduled.

3.f Prior and Concomitant Therapy

Patients will receive induction therapy with either anti-thymocyte globulin or basiliximab at the time of transplantation. Depending on patient's prior medical history, they may have had prior immunosuppression and may be on immunosuppression prior to their transplant. This will not interfere with the study protocol or eligibility except if they meet exclusion criteria.

3.g Packaging

Study drugs will be packaged according to standard procedures for the medication.

3.h Blinding of Study Drug

This is an open label pilot study. The patients and study members will not be blinded to the study drug.

3.i Receiving, Storage, Dispensing and Return

Study medications may be self-administered by the patient. Study medications may be administered at the study site or ordered through patient's preferred pharmacy.

F Study Procedures

F1 Screening for Eligibility

Patients may be screened by appropriate study team members such as clinical coordinators. Patient enrollement will be determined from study inclusion and exclusion criteria (Section E2).

F2 Schedule of Measurements

See Flowsheet for study procedure/measurements
See individual attached Visit 0-6 for checklists

F3 Visit 00 – post transplantation (prior to discharge)

- Inclusion/Exclusion checklist
- Informed consent obtained
- Contact and Demographics Information form filled
- Medical history collected
- Physical Exam
- Pill Manager by Medisafe downloaded and explained
- Dosages given and recorded

F4 Visit 01 – 2-4 weeks after transplant surgery

- Verbally agreed to continue participation in study
- Was re-consent if needed
- Medical history collected
- Evaluated for AEs
- Physical Exam
- Laboratory tests performed and recorded
- Dosages updated and recorded

F5 Visit 02 – 5-8 weeks after transplant

- Verbally agreed to continue participation in study
- Was re-consent needed?
- Medical history collected
- Evaluated for AEs
- Physical Exam

- Laboratory tests performed and recorded
- Dosages updated and recorded

F6 Visit 03 – 12 weeks post transplant

- Verbally agreed to continue participation in study
- Was re-consent needed?
- Medical history collected
- Evaluated for AEs
- Physical Exam
- Laboratory tests performed and recorded
- Dosages updated and recorded
- Pill Manager by Medisafe records emailed
- BAASIS Survey distributed

F7 Visit 04 - 6 months post transplant

- Verbally agreed to continue participation in study
- Was re-consent needed?
- Medical history collected
- Evaluated for AEs
- Physical Exam
- Laboratory tests performed and recorded
- Dosages updated and recorded

F8 Visit 05 – 9 months post transplant

- Verbally agreed to continue participation in study
- Was re-consent needed?
- Medical history collected
- Evaluated for AEs
- Physical Exam
- Laboratory tests performed and recorded
- Dosages updated and recorded

F9 Visit 06 – 12 months post transplant

- End of Study/Early Termination form completed
- Was re-consent needed?
- Medical history collected
- Evaluated for AEs
- Physical Exam
- Laboratory tests performed and recorded
- Dosages updated and recorded
- Pill Manager by Medisafe records emailed
- BAASIS Survey distributed

F10 Safety and Adverse Events

Monitored throughout the study.

10.a Safety and Compliance Monitoring

At each study visit, we will collect the data as described in the study table and in the protocol description. The PI or study staff will review the data on an ongoing basis and every quarter for accuracy and completeness. Adverse effects will be routinely reviewed and recorded at each visit. Additionally any adverse event reported to the transplant physician, transplant coordinator or study coordinator including emergency department evaluation and/or hospitalization will be reviewed and documented by the principal investigator. Adverse event reporting will be done per the study agreement.
The study team will meet quarterly to review outcomes and safety of patients enrolled in the study as well as AEs. SAEs will be reviewed per occurrence.

Data on adherence to the treatment protocol may be collected via surveys and on Pill Reminder by Medisafe (emailed to research staff) at months 3 and 12. Adherence will be reviewed quarterly by the PI and the study statistician.

10.b Medical Monitoring

i Investigator and research team only

Both arms will follow the standard protocol visits in our clinics and will be seen at week 2-4, week 5-8, week 9-12, month 6, 9, and 12 (all +/- 2 weeks). These visits will include a focused physician exam, evaluation of adverse events as defined by the Common Toxicity Criteria of the National Cancer Institute and assessment of the patient's Immunosuppression. Labs are followed as per the center standard protocol and will be performed at the patients' designated lab outpatient.

10.c Definitions of Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events

include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

[Code of Federal Regulations]
[Title 21, Volume 5]
[Revised as of April 1, 2017]
[CITE: 21CFR312.32]

10.d Classification of Events

i Relationship

Relationship of adverse events to the study medication will be decided upon by the PI.

ii Severity

Severity of adverse events will be decided using the Common Terminology Criteria for Adverse Events (CTCAE).

iii Expectedness of side effects to medications and adverse events

There are known common side effects to each medication. Tacrolimus has known side effects of tremors, sleep difficulty irregardless of its therapeutic range. Other side effects such as electrolyte abnormality in hyperkalemia, hypertension, and increased creatinine (if above therapeutic range) are known side effects as well. Both azathioprine and mycophenolate mofetil/mycophenolic acid have side effect of leukopenia and anemia. Azathioprine can also have elevated liver enzymes as a rarer side effect. Mycophenolate mofetil/mycophenolic acid have a known side effect of gastrointestinal upset or diarrhea.

10.e Data Collection Procedures for Adverse Events

At each study visit, we will collect the data as described in the study table and in the protocol description. The PI or study staff will review the data on an ongoing basis and every quarter for accuracy and completeness. Adverse effects will be routinely reviewed and recorded at each visit. Additionally any adverse event reported to the transplant physician, transplant coordinator or study coordinator including emergency department evaluation and/or hospitalization will be reviewed and documented by the principal investigator. Adverse event reporting will be done per the study agreement.
The study team will meet quarterly to review outcomes and safety of patients enrolled in the study as well as AEs. SAEs will be reviewed per occurrence.

10.f Reporting Procedures

Adverse events will be recorded at each medical visit. With the occurance of an AE, an Adverse Event Log will be filed for the patient and put up for review by the PI.

In the instance of a SAE, an Serious Adverse Event Log will be filed and shown to the PI with every occurance.

10.g Adverse Event Reporting Period

AEs will be reported to the IRB at the time of continuing review. SAEs will be reported according to IRB policy.

F11 Study Outcome Measurements and Ascertainment

- Acute Rejection:

We do not perform a protocol biopsy in our center, however, we have a low threshold to do a biopsy if there is an increased creatinine, proteinuria (urine protein/ creatinine > 1 gram), or de novo DSA with high level MFI. The decision of the biopsy will be based on the decision of the clinician.

- Graft Failure: Graft failure will be defined by the return to hemodialysis, re-transplantation, or patient death. Death-censored graft failure will be defined as the return to hemodialysis or re-transplantation.

- Adherence:

App: We will use “Pill Manager by Medisafe” for recipients who have I-phone or android smart device. Installing the app will take place before discharge. Records from the smart phone will be emailed from the device at the clinic visit at months 3 and 12.

Survey: Survey will be distributed at months 3 and 12. Other surveys will be also distributed to examine any possible side effects.

Tacrolimus level variability: Average variability in tacrolimus levels for the follow-up period preceding each of the surveys will also be calculated and compared between the two groups

Antimetabolite refill records:
Pharmacies will be contacted to assess for timing between refills to ensure that patients have taken medication as scheduled.

Additionally, CBC, BMP or Renal panel (including creatinine, eGFR) Tac trough levels will be checked once a week for the first four months then once every other weeks as part of standard of care labs post transplant. These will be collected as data points during the study duration.

G Statistical Plan

G1 Sample Size Determination and Power

This is a pilot study. The number of patients was chosen to see if any initial evidence can be found for further investigatrion.

G2 Analysis Plan & Statistical Methods

Recipient characteristics will be described using proportions for categorical variables, and means with standard deviations for continuous variables. Recipient and donor factors will be compared among the groups (one a day medication group vs twice a day medication group) using a $\chi 2$ or Fisher test for categorical variables and analysis of variance test or Kruskal Wallis tests for continuous variables, depending on the distribution of the variable.

Allograft and recipient survival will be assessed using the Kaplan-Meier survival analysis, and P values will be calculated using the log-rank test. Multivariate analysis using the Cox model will be used to calculate the hazard ratio during the follow up period for allograft failure and recipient death.

Adherence will be divided according to the level of adherence (score) into tertiles. Logistic regression will be used to examine the association between adherence and the medications group.

H Data Handling and Record Keeping

H1 Confidentiality and Security

Subject privacy: During the study we will perform medical history and examination at each recurring visit as part of standard follow-up and usual care post-transplant. Labs will be done per standard of care, and collected at each time point until 12 months post-transplant. All information collected will be for research purposes only and data will be kept in strict confidence. No information will be given to another party without the consent of the subject. We will be assigning patients a unique study number for de-identification purposes.

Database protection: We will be keeping a database that will be secured with password protection. The person performing statistics will be receiving only de-identified information from the database. For paper documents such as source documents and questionnaires, these will be kept in separate participant charts that will be secured in a locked cabinet in the locked study coordinator office with access only for study personnel.

H2 Training

All lab personel will be qualified to do their assigned work. All personel working with PHI will have documented HIPAA training. Each team member will be noted on the Department Signature Sheet.

H3 Case Report Forms and Source Documents

CRFs will be created and kept in each person's file, tracking medications, FK levels, labs, and information regarding medication refills (See all attachments). All source documents including labs near the time of each scheduled visit that patients get outpatient, surveys, medication adherence pill monitoring system information, outpatient notes will be placed into each person's file.

H4 Records Retention

All research records, including signed consent forms, will be kept in their original form or a certified scanned electronic form for at least seven years beyond close of the study.

I Study Monitoring, Auditing, and Inspecting

I1 Study Monitoring Plan

The PI and study members will review the data on an ongoing basis and every quarter for accuracy and completeness.

J Study Administration

J1 Organization and Participating Centers

This study will be performed at Washington University School of Medicine.

J2 Funding Source and Conflicts of Interest

This study is funded by Veloxis Pharmaceuticals. Each study team member will declare any conflicts of interest to the IRB.

J3 Subject Stipends or Payments

Participants will not receive any payment for the study nor study medication, which patients will receive through their insurance coverage.

J4 Study Timetable – Table 1

Study event	Visit number						
	Visit 0 – post surgery	Visit 1-2-4 weeks	Visit 2 – 5-8 weeks	Visit 3 – 9-12 weeks	Visit 4 – 6 months	Visit 5 – 9 months	Visit 6 – 12 months
Inclusion/Exclusion	X						
Informed consent	X						
Contact/demographics	X						
Medical history	X						
Physical exam	X						
Medisafe med manager taught	x						
Med dosages given/recorded	x						

Patient verbal consent to continue study		X	X	X	X	X	X
Reconsent if needed		X	X	X	X	X	X
Evaluate for AEs		X	X	X	X	X	X
Lab tests recorded from most recent labs	X	X	X	X	X	X	X
Med doses updated and recorded		x	X	X	X	X	X
Medisafe records obtained		X	x	X	x	X	X
Survey completed				x			X
End of study/Termination form completed							X

Figure 1. Timeline of study procedures.

K Publication Plan

We plan to submit abstracts on the results of our study to the following meetings: American Transplant Congress and American Society of Nephrology meetings. We plan to publish our results in one of the following journals: American Journal of Transplantation, Transplantation, Clinical Transplantation, Transplant International, NDT after completion of the study and final analysis of study results.

L Attachments

L1 Tables

Table 1 – study timeline

L2 Informed consent documents

See attached

L3 Questionnaires or surveys

See attached BAASIS survey used for 3 and 12 month

M References

Budde, K., Bunnapradist, S., Grinyo, J. M., Ciechanowski, K., Denny, J. E., Silva, H. T., … Envarsus study group. (2014). Novel Once-Daily Extended-Release Tacrolimus (LCPT) Versus Twice-Daily Tacrolimus in de novo Kidney Transplants: One-Year Results of Phase III, Double-Blind, Randomized Trial. *American Journal of Transplantation*, *14*(12), 2796–2806. https://doi.org/10.1111/ajt.12955

Bunnapradist, S., Ciechanowski, K., West-Thielke, P., Mulgaonkar, S., Rostaing, L., Vasudev, B., … MELT investigators. (2013). Conversion From Twice-Daily Tacrolimus to Once-Daily Extended Release Tacrolimus (LCPT): The Phase III Randomized MELT Trial. *American Journal of Transplantation*, *13*(3), 760–769. https://doi.org/10.1111/ajt.12035

Jamieson, N. J., Hanson, C. S., Josephson, M. A., Gordon, E. J., Craig, J. C., Halleck, F., … Tong, A. (2016). Motivations, Challenges, and Attitudes to Self-management in Kidney Transplant Recipients: A Systematic Review of Qualitative Studies. *American Journal of Kidney Diseases*, *67*(3), 461–478. https://doi.org/10.1053/J.AJKD.2015.07.030

Laliberté, F., Nelson, W. W., Lefebvre, P., Schein, J. R., Rondeau-Leclaire, J., & Duh, M. S. (2012). Impact of Daily Dosing Frequency on Adherence to Chronic Medications Among Nonvalvular Atrial Fibrillation Patients. *Advances in Therapy*, *29*(8), 675–690. https://doi.org/10.1007/s12325-012-0040-x

Rostaing, L., Bunnapradist, S., Grinyó, J. M., Ciechanowski, K., Denny, J. E., Silva, H. T., … Parmjeet, R. (2016). Novel Once-Daily Extended-Release Tacrolimus Versus Twice-Daily Tacrolimus in De Novo Kidney Transplant Recipients: Two-Year Results of Phase 3, Double-Blind, Randomized Trial. *American Journal of Kidney Diseases*, *67*(4), 648–659. https://doi.org/10.1053/J.AJKD.2015.10.024

Vrijens, B., & Heidbuchel, H. (2015). Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence. *Europace*, *17*(4), 514–523. https://doi.org/10.1093/europace/euu311