Clinical Study Protocol

A prospective, open label, pilot study comparing the use of low-target Advagraf with rabbit antithymocyte globulin induction versus conventional target Advagraf with basiliximab induction in a steroid-avoidance immunosuppressive protocol for de novo renal transplant recipients

Principal Investigator(s): Jagbir Gill, MD MPH

Co-Investigator(s): John Gill, MD MS

Olwyn Johnston, MD MS

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Ethics and Good Clinical Practice

This study will be performed according to the principles of Good Clinical Practice [Chapter 2 of the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP)], the declaration of Helsinki, and national laws and regulations about clinical studies. The study may not start without written Ethics approval and the written informed consent of the patient.

1. Title of Study

A randomized prospective open label pilot study comparing the use of low-target versus conventional dose tacrolimus (Advagraf) dosing in a steroid-avoidance immunosuppressive protocol for de novo adult, non-diabetic, low immunological risk, kidney only transplant recipients.

2. Introduction and Rationale

Kidney transplantation is the treatment of choice for patients with end stage renal disease (ESRD) and is associated with a significant increase in life expectancy(1, 2). In the current era of immunosuppressant therapy, rates of acute rejection and early graft loss have improved dramatically. However, significant improvements in long-term patient and allograft survival have not been achieved.

Long-term outcomes are limited, in part, by high rates of cardiovascular disease and new onset diabetes after transplantation (NODAT). Both corticosteroids and calcineurin inhibitors (CNI) significantly contribute to these problems and the desire to minimize these effects has led to the advent of immunosuppressant protocols that limit exposure to these agents(3-7).

In the ELITE-Symphony trial, a maintenance protocol of Mycophenolate mofetil (MMF), low-dose tacrolimus, and corticosteroids was found to be advantageous for renal function, allograft survival, and acute rejection rates(8). A slight reduction in the rate of NODAT was reported between standard dose cyclosporine (6.4%) and low-dose cyclosporine (4.7%) in this trial. However, given the lower risks of biopsy proven acute rejection reported in the low-dose tacrolimus arm, the authors concluded that it may be feasible to further reduce the risk of NODAT with a reduction in corticosteroid exposure in the setting of low-dose tacrolimus.

Existing data on corticosteroid withdrawal or avoidance strategies report a higher risk of acute rejection(9-11) but have failed to demonstrate a significant difference in graft survival between steroid free and steroid-based protocols(12-14). A number of studies have also demonstrated a lower risk of cardiovascular risk factors, such as hypertension with steroid withdrawal or avoidance(9, 14, 15). However, disappointingly NODAT remains a significant problem in corticosteroid withdrawal protocols. In a 5-year multicenter randomized trial comparing early steroid withdrawal with a steroid-based maintenance protocol

Woodle et al. reported an incidence of NODAT of 21.5%, with no significant difference between patients withdrawn from steroids versus those maintained on low dose steroids(10). The high incidence of NODAT in the steroid avoidance arm of this study may, in part, be attributed to the high doses of tacrolimus used. During the first year post-transplant, serum tacrolimus levels were largely maintained above 10ng/ml in this study and may have contributed to a greater incidence of NODAT.

The St. Paul's Hospital and Vancouver Hospital programs have employed an early steroid withdrawal protocol, with basiliximab induction and standard dose calcineurin inhibitor for low immunologic risk transplant recipients for a number of years and remain the sole transplant programs in Canada using such a protocol. With this protocol we recognize an acute rejection rate of approximately 20%, and a NODAT rate of approximately 30%.

We hypothesize, that a combined approach of early steroid withdrawal and low dose tacrolimus (Advagraf) for low immunologic risk transplant recipients will be effective in reducing the incidence of NODAT, while maintaining a low risk of acute rejection.

We propose a pilot study to compare early post-transplant outcomes among low immunologic risk kidney transplant recipients undergoing early corticosteroid withdrawal in conjuction with **low-target** tacrolimus (Advagraf) versus **standard target** tacrolimus (Advagraf).

3. Study Objectives

Hypothesis:

Objectives: The objective of this study is to compare early post-transplant outcomes with the use of low target versus standard target Advagraf in *de novo* kidney allograft recipients of low immunologic risk undergoing early corticosteroid withdrawal.

Hypothesis: Low target Advagraf in the setting of early corticosteroid withdrawal will be associated with equivalent rates of acute rejection, graft loss, and patient death, but lower rates of NODAT, compared to standard target Advagraf.

Primary Outcome

Composite endpoint of biopsy proven acute rejection and NODAT at 6 months post transplantation. NODAT will be defined as either FPG $\geq$7.0mmol/L OR symptoms of hyperglycemia and a random plasma glucose of $\geq$11.1 OR 2-h plasma glucose >11.1 during an OGTT.

Secondary Outcomes

- Patient survival

- Graft survival
- Frequency, severity, and treatment of hypertension
- Frequency, severity, and treatment of hyperlipidemia (serum total cholesterol, HDL, LDL, and triglycerides)
- Weight gain
- Infections (CMV, opportunistic infections including urinary tract infections requiring treatment, pneumonia)
- Malignancy, including PTLD
- Leukopenia
- Renal function as measured by serum creatinine and MDRD eGFR
- Therapy with anti-diabetic medications beyond 1 month post transplant

4. Investigational Plan

4.1 Overall study design

The study will take place at St. Paul's Hospital and Vancouver Hospital, which together perform approximately 150 kidney transplants per year. Before any study-related evaluations are performed, the patient must give written informed consent.

A total of 34 patients who meet the inclusion criteria will be randomized into 2 groups prior to transplantation:

Group A will receive rabbit anti-thymocyte globulin (rATG) induction (3 doses of 1.5 mg/kg during the first post transplant week) with IV solumedrol, MPA (Mycophenolate Mofetil or Mycophenolate Sodium), and "low-target" Advagraf.

Group B will receive basiliximab induction (40 mg total) with IV solumedrol, MPA (Mycophenolate Mofetil or Mycophenolate Sodium), and "standard target" Advagraf.

Figure 1 outlines the study design and Table 1 outlines target serum Advagraf levels for each study group. In both groups patients will not receive maintenance corticosteroids and will be steroid free by day 14 post transplant. During the 6 month treatment period, patients will be seen by study coordinators at baseline, 1 month, 3 months, and 6 months post transplant.

Figure 1 Study design

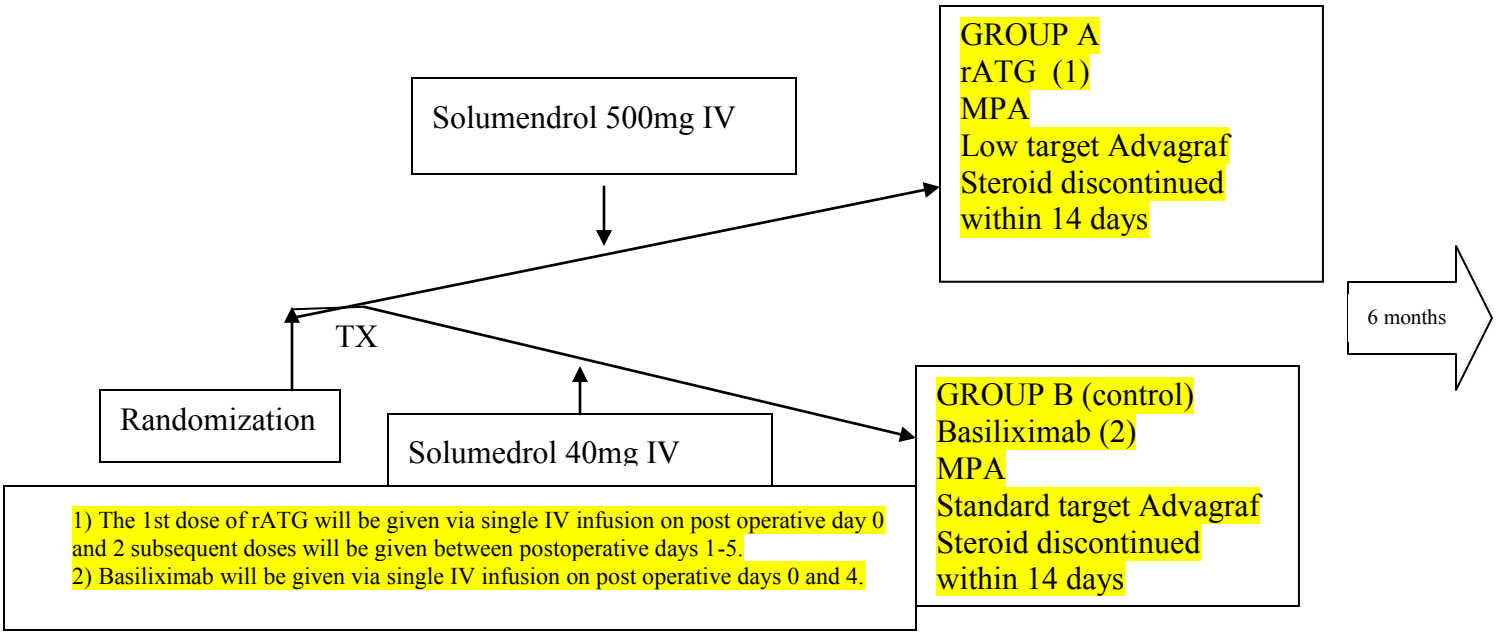

Table 1. Target Advagraf (tacrolimus) serum trough levels

Low Target (Group A)		**Standard Target (Group B)**	
Months post tx	Level	Months post tx	Level
0-1 month	5-7	0-1 month	8-12
1-3 months	4-5	1-3 months	6-9
3-6 months	3-4	3-6 months	5-8

4.2. Discussion of design

The purpose of this study is to compare early post transplant outcomes with low-target versus standard target Advagraf. The optimal induction agent has not been established in steroid free protocols. A secondary analysis of the Astellas sponsored double-blinded study suggested a lower acute rejection rate with

rATG and it would appear that most centers are using rATG induction in this setting. As immunosuppressant protocols typically involve a combination of drugs, we have elected to use rATG in our low CNI exposure group in order to avoid any increased risk of rejection. We expect rATG will ensure no increase in acute rejection rates in the low target Advagraf group, but expect it will have no impact on the incidence of NODAT.

In view of the exploratory nature of this study a randomized, open-label pilot study is appropriate and blinding of Advagraf doses would be extremely difficult.

4.3. Study population

4.3.1 Patient population

All kidney-only living and deceased donor transplant recipients at St. Paul's Hospital and Vancouver Hospital, aged over 18 years, with a current peak PRA<30%, and no evidence of diabetes mellitus (defined as no documented history of diabetes mellitus or the use of diabetic medications, and a random plasma glucose measurement <11.1 at the time of transplantation) are eligible for participation in the study.

4.3.2. Sample Size

For this pilot study, we aim to recruit a total of 34 subjects.

After receiving informed consent, subjects will be randomized on a 1:1 basis to one of the two treatment groups. Subjects who discontinue the study prematurely will not be replaced.

4.3.3. Inclusion and exclusion criteria

Each patient must meet all of the following inclusion criteria, and none of the following exclusion criteria in order to participate in this study.

Inclusion criteria

1 Male or female patients over 18 years of age who receive a deceased, living unrelated or living related donor renal transplant
2 No history of pre-existing diabetes mellitus
3 Not using diabetic medications (insulin, hypoglycemic agents) at the time of transplantation
4 Random plasma glucose level <11.1 at the time of transplantation
5 Peak PRA<30%
6 Females capable of becoming pregnant must have a negative pregnancy test at baseline and are required to practice an approved method of birth control for the duration of the study and for a period of three months following discontinuation of study medication
7 The patient has given written informed consent to participate in the study

Exclusion criteria

Patients meeting any of the following criteria at baseline will be excluded from study participation.

1 Patients with primary non-function
2 Peak PRA>= 30%
3 Multiple organ transplants
4 HLA identical living donor transplant recipients
5 Cold ischemia time over 24 hours
6 Nonheart beating donor kidney recipients
7 Pediatric donor kidney recipients
8 Donor age>=60 years
9 Patients who are known to have a positive hepatitis C serology, who are human immunodeficiency virus (HIV) or Hepatitis B surface antigen positive. Laboratory results obtained within 6 months prior to study entry are acceptable. Recipients of organs from donors who test positive for Hepatitis B surface antigen or Hepatitis C will be excluded.
10 Patients who are Epstein–Barr virus (EBV) negative and are receiving a transplant from an EBV-positive donor (mismatch).
11 Presence of any severe allergy requiring acute (within 4 weeks of baseline) or chronic treatment, or hypersensitivity to drugs similar to those used in the study
12 Patients with systemic infections
13 Existence of any surgical or medical condition, other than the current transplant, which in the opinion of the investigator, preclude enrollment in this trial

4.3.4 Discontinuation of study

Prednisone will be routinely withdrawn within 5 days post transplant as per clinical protocol, but may be continued for up to two weeks post transplant if clinically indicated. In cases where prednisone use exceeds 2 weeks, the subject will be deemed in violation of the study protocol and excluded from participation in the study.

In the absence of a medical contraindication or significant protocol violation, every effort will be made by the Principal Investigators to continue the patient on study medications.

It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued the reason will be recorded.

4.4. Treatment

4.4.1 Treatment assignment

Patients who fulfill all inclusion/exclusion criteria within the baseline period, will be asked for written consent to participate in the study. Each patient will be assigned a unique identification number. Randomization will be 1:1 and stratified by donor type (living, deceased).

4.4.2 Treatment Agents:

1. Advagraf (0.25mg/kg) orally once daily dosed as per manufacturer's recommendation to target trough levels as per Table 1
2. Mycophenolate Mofetil (1g BID) or Mycophenolate Sodium (720mg BID)
3. Basiliximab 20mg IV on post-operative days 0 and 4
4. Rabbit antithymocyte globulin (total dose 4.5-6.0 mg/kg)
5. Solumedrol 500mg IV at the time of transplantation, followed by methylprednisilone/prednisone to be discontinued within 14 days of transplantation

During the study period Advagraf dosage will be adjusted according to manufacturer recommendations to achieve target levels in each group (Table 1). As per standard clinical practice the use of mycophenolate mofetil and mycophenolate sodium is interchangeable. Mycophenolate use will be tailored based on routine clinical practice. At completion of the study, patients will remain on their prescribed maintenance immunosuppressive protocol, consisting of Advagraf and Mycophenolate.

4.4.3 Concomitant therapy

No medication other than the study drugs and the usual medications of the patients should be given during the full treatment period of the study, i.e., from the initial day of screening until all of the final study evaluations have been completed. Exceptions to this rule apply to medication which may be needed to treat adverse events. The administration of any additional medication (including over-the-counter medications and vitamins) will be clearly documented.

All immunosuppressive drugs other than those specified by protocol are disallowed. Permissible anti-rejection therapy includes methylprednisolone, antilymphocyte, and antibody therapy according to local practice.

4.5 Visit schedule and assessments

4.5.1. Visit schedule

Patients will be encouraged to attend all evaluations as scheduled. However, visit windows of ± 2 days for Week 1, ± 3 days for remaining weekly or semiweekly visits, and ± 7 days for monthly visits will be allowed. Patients will be seen and evaluated in accordance with the study evaluation schedule.

Baseline

All baseline assessments, including obtaining written informed consent, will be performed prior to the transplant. Laboratory evaluations at baseline will be performed by the local laboratory. The patient's medical history and transplant information will be reviewed. The patient's vital signs and physical exam will provide documentary evidence that the patient is in stable condition and not suffering from any disqualifying condition.

Evaluation and visit schedule

Visit Timepoint	**Baseline**[1]	**1**[2]	**3**	**6**
Visit Number	**1**	**2**	**3**	**4**
Informed Consent	X			
Randomization	X			
Background information – recipient	X			
Demography + Relevant medical history/Current medical conditions	X			
Physical examination	X			
Vital signs and clinical assessment	X	X	X	X
Laboratory test (local) [3]	X	X	X	X
Immunosuppressive medications	As per protocol			
Kidney allograft biopsy	As needed per clinical practice			
Follow up		Complete at 6 months		
Study Completion				X

[1] Baseline visit will occur pre-operatively

[2] The 1st follow up visit will be 1 month post transplant

[3] Drug levels will be monitored on a frequency based on routine clinical practice. Serum chemistry will be assessed as per routine clinical management post transplant.

A Hemoglobin A1c test will be performed at each post transplant visit and be included in their regular clinic work. An Oral Glucose Tolerance Test will be performed at 6 months only if the patient is displaying borderline symptoms of NODAT as determined by an investigator.

Study duration: We plan to enroll the first patient by September 1st, 2010. Last patient visit will be enrolled by December 31, 2017

5. Data management and statistical methods

This is a pilot study. Primary and secondary endpoints are stated previously in the proposal. The primary endpoint will be evaluated by time-to-event Kaplan Meier analysis and by Chi-squared analysis of final 6 month data.

6. References

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