A Single Center, Randomized, Double-Blind Controlled Trial of Sitagliptin Versus Placebo to Reduce the Incidence and Severity of New-onset Diabetes After Kidney Transplant

March 11, 2015 Protocol # 50669 Version 6

Study protocol and Statistical Analysis Plan

Inclusion/Exclusion

Inclusion criteria

1. Adult (≥18 yo) recipient of living-donor or deceased donor kidney transplant
2. Blood sugar ≥ 200 mg/dL in first 120 hours after transplant
3. No history of diabetes or prior treatment with insulin or oral hypoglycemic agents

Exclusion criteria

1. A1c of ≥6.5% measured immediately pre-transplant
2. Recipient of simultaneous kidney-pancreas, kidney-liver, kidney-heart, or kidney-lung transplant
3. Prior non-renal solid organ transplant

Study procedures

Sitagliptin dosing

In patients randomized to sitagliptin, the initial dose will be 100mg oral per day, adjusted based on creatinine clearance per prescribing information (9):

Creatinine clearance (mL/min)	Sitagliptin dose (mg orally per day)
≥ 50	100
≥30 and <50	50
<30 or on dialysis	25

Screening period (Visit 1)

All patients presenting for living-donor or deceased donor kidney transplant will have a medical history, medication history, vital signs, height, weight, body mass index, physical exam, random blood sugar, HbA1c and EKG done as part of routine pre-transplant protocol at Barnes Jewish Hospital. Patients with hyperglycemia, defined as a random blood sugar ≥ 200 mg/dL, in the first 120 hours after kidney transplant will be screened to determine eligibility for the study based on inclusion and exclusion criteria.

Randomization (Visit 2)

Patients meeting study entry criteria and consenting to study participation will be stratified based on HbA1c (<5.7 or 5.7-6.4%) and block randomized in blocks of eight in a 1:1 ratio to sitagliptin versus placebo. Sitagliptin dose will be 100mg/day, adjusted per creatinine clearance and tolerability. A fasting blood sugar will be obtained prior to initiation of sitagliptin. Patients will be instructed by a licensed diabetic educator on proper measurement and recording of fasting and post-prandial blood sugars. Subjects will be provided a log, standard glucometer and testing strips to maintain a blood sugar log post-discharge. Visit 2 will occur within 24 hours after Visit 1.

Drug dosing period (Visits 3-4)

Sitagliptin or placebo will be continued until 3 months post-transplant, at which time study medication will be discontinued and collected from the subject. At the 1 and 3 month visits, vital signs, height, weight, and BMI will be obtained. A physical exam will be performed. Blood sugar logs provided by the patient will be reviewed and adverse effects recorded. At the 3 month visit (Visit 4), a HbA1c, 2-hour OGTT, fasting C-peptide and insulin level will be obtained.

Follow-up (Visit 5)

At the 6 month final visit, 3 months following discontinuation of study medication, vital signs, height, weight, BMI, HbA1c, 2-hour OGTT, fasting C-peptide and insulin level will be obtained. A physical exam will be performed. Blood sugar logs provided by the patient will be reviewed and adverse effects recorded.

Efficacy Assessment

Efficacy assessment

Efficacy of sitagliptin versus placebo in 1) lowering 2-hour OGTT by ≥ 20 mg/dL, 2) preventing NODAT defined by normal 2-hour OGTT and 3) improving HbA1c by ≥0.5% will be assessed at 3 months post-transplant.

Statistical analysis

The following testing methods will be used in the study:

Statistical methods

Oral Glucose tolerance test – T-test or Mann-Whitney U

Hemoglobin A1c – T-test or Mann-Whitney U

Power/Sample size:

Based on a sample size of 25 patients per group, this study has over 80.7% power to detect a difference of 20 mg/dL in 2-hour OGTT. This calculation assumes a standard deviation of 25 mg/dL or less between groups. However to account for study drop out and loss to follow-up (those who did not take study drug or did not come for follow-up), the study expanded to include 61 patients.