Centre intégré
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et de services sociaux
de l'Est-de-
l'Île-de-Montréal

Québec

Protocol Title : A prospective clinical study to evaluate the effect of weight loss through bariatric surgery, laparoscopic sleeve gastrectomy, on the pharmacokinetics of immunosuppressive medications in morbidly obese candidates for renal transplantation

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Clinical Study Protocol

A prospective, clinical study of the effect of laparoscopic sleeve gastrectomy on the pharmacokinetics of immunosuppressive drugs in the morbidly obese, kidney transplant candidate.

Protocol #1

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Revision 1:

Protocol synopsis

Title of study: Prospective, clinical study of the effect of bariatric surgery, laparoscopic sleeve gastrectomy, on the pharmacokinetics of immunosuppressive drugs in the morbidly obese, kidney transplant candidate.

Objectives:

Primary

1- Evaluate the possible changes in the pharmacokinetics of oral immunosuppressive medications due to bariatric surgery, comparing pre-bariatric surgery to 12 months post-operative.

2- Evaluate the degree of weight loss achieved after bariatric surgery in the chronic renal failure patient.

3- Evaluate the change in general quality of life score, SF-36, at baseline pre-bariatric surgery versus 12 months post-bariatric surgery.

Secondary

There are three secondary objectives. The first of these is to evaluate changes to residual renal function in the **pre-dialysis** renal transplant candidate, at baseline versus month 12 post-bariatric surgery. Second, evaluate the change in the number and dose of medications required to treat co-morbidities including, hypertension, hyperlipidemia and diabetes mellitus. Third, the incidence of complications 1, 6 and 12 months post-bariatric surgery will be evaluated.

Study Rationale:

Morbid obesity is a growing epidemic in Canada and particularly in the kidney transplant patient. It is a known risk factor for increased peri-operative complications, worse long-term graft function and worse patient survival. As a result, almost all transplant centres in Canada have imposed a maximum

limit for the body mass index (BMI) for acceptance to the waiting list. However, at the same time, the ability of this patient population to lose the excess weight through nutritional modifications and physical exercise is severely limited due to the constraints of renal disease such as its dietary limitations, and the chronic malaise and fatigue of dialysis. If these patients are denied transplantation due to morbid obesity, a reasonable and effective treatment plan must be offered to provide any hope of life-saving kidney transplantation.

A few small retrospective case series have reported the efficacy of bariatric surgery in the pre- and post-transplant populations. Scarce data have been reported on the effect of bariatric surgery on immunosuppressive medication, in particular, the bioavailability. Prospective data is required to define the safety, efficacy and role of bariatric surgery in the management of morbidly obese kidney transplant candidates. It is also important to determine which operation would be safest.

Currently, sleeve gastrectomy represents a restrictive operation that avoids the foreign body of a gastric band and the malabsorption of operations such as Roux-en-Y gastric bypass or duodenal switch. Performed by laparoscopy, it can provide effective weight loss in the moderate category of morbid obesity (BMI: 40 - 50 kg/m^2) and should theoretically have little impact on the pharmacokinetics of the immunosuppressive medications, in comparison to the malabsorptive bypass procedures, such as the duodenal switch or the Roux-en-Y gastric bypass. This study will focus on pre-transplant chronic renal failure patients to address the obesity prior to the transplantation, in an effort to reduce the future risks of peri-transplant complications and to optimize the graft and recipient outcomes.

A standard regimen of immunosuppression usually includes tacrolimus, mycophenolate mofetil (MMF) and prednisone. Though practical dosing of tacrolimus is routinely gauged by trough levels of the twice-a-day dosing, pharmacokinetics studies including an $AUC_{0\text{-}12\ hours}$ and a C_{max} are of particular interest in judging the pharmacokinetic and adverse effect profile.

The absorption of tacrolimus normally occurs in the duodenum but secondary absorption occurs also in the small intestine and the colon. With regards to MMF, the measurement of plasma MPA $AUC_{0\text{-}12\ hours}$ is the most accurate way to determine MPA exposure in renal transplant patients. An AUC in the range of 30 to 60 μg*h/mL has been described as the target to maximize immunosuppression while minimizing MPA-related side effects. Absorption of MMF normally occurs in the stomach and duodenum. More recently, extended release formulations of tacrolimus and an enteric-coated version

of mycophenolate acid have come into use clinically to provide more stable absorption curves and fewer adverse events.

Methodology:

The study is a single centre prospective study of 20 patients.

The inclusion criteria are adult (>18 years), stage IV and V chronic renal disease (glomerular filtration rate < 30 ml/min, based on estimated GFR as determined by the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation) and a body mass index (BMI) of greater than 40 kg/m^2. The patients will be included into two sub-groups, pre-dialysis and dialysis. All patients will be identified during the assessment for kidney transplantation and from the pre-dialysis clinic. The exclusion criteria will include patients awaiting potential multi-organ transplantation, pregnancy, active infection and a history of active gastric disease or gastric operation that would preclude a bariatric surgery. Patients with a known intolerance of the study drugs and those who are not surgical candidates will also be excluded. All patients who meet the inclusion criteria and consent to enter the study will enter the preliminary group of Medical Management.

A baseline consultation and investigations will be made to determine their eligibility for the study. A consultation with a nutritionist will be performed to ensure compliance with the dietary restrictions of renal disease, diabetes, arterial hypertension and dyslipidemia, as applicable. Modifications will be made according to individual needs with a clear effort to identify and reduce excess daily caloric intake. A physical exercise plan will be made with the patient to include daily use of a stationary bicycle, or an equivalent, with a gradual augmentation of effort and time according to tolerance. A targeted BMI will be identified to reach a BMI < 36.0 kg/m^2 at a minimum weight loss rate of 2 kg/month. Consultations with an endocrinologist and a cardiologist will be used to optimize treatment of diabetes and heart disease respectively as required. Clinical follow-up will be performed at three month intervals while part of the study.

The baseline investigations will include a complete blood count (leukocytes, hemoglobin, platelets, mean corpuscular volume), electrolytes (serum sodium, potassium, chloride, magnesium, calcium, bicarbonate), liver function tests (AST, ALT, alkaline phosphatase, bilirubin, albumin, prealbumin), renal function (serum creatinine, urea), coagulation profile (partial thromboplastin time, INR), lipid

profile (LDL, HDL, cholesterol), nutritional profile (ferritin, vitamins B1, B6, and B12, calcium, 25-OH-vitaminD, parathyroid hormone (PTH), folic acid, zinc) and others including TSH, a 24-hour urine creatinine clearance (if pre-dialysis) and Hb_{A1C} and fasting blood glucose. Physical examination will include vital signs and an obesity profile (height, weight and abdominal circumference at the level of the anterior superior iliac spine). The average daily insulin requirements will be recorded. Quality of life will be assessed by the SF-36 short form.

At the each follow-up visit (every three months), obesity will be assessed and if weight loss is less than 2 kg/month after 6 months, a consultation with the bariatric surgeon will be made. If the decision is made to proceed to a laparoscopic sleeve gastrectomy by an independent bariatric surgeon, the patient will be entered into the intervention group, Bariatric Surgery. This group of patients will undergo pharmacokinetic analysis prior to the bariatric surgery and entered into the study. In addition, clinical follow-up will include blood analyses, physical examination and QOL questionnaire. Any patient, who do not consent to or are refused for bariatric surgery, will continue to be followed in the Medical Management Group.

Pharmacokinetics will be analysed two months prior to bariatric surgery and one year afterwards. The patients will undergo two separate analyses pre-bariatric surgery and two separate analyses post-bariatric surgery. The patients will receive oral tacrolimus 3 mg (taken on an empty stomach, 1 hour prior to the standardized breakfast) and enteric coated mycophenolate acid OD 720 mg, beginning the morning of testing. The plasma levels of MPA, measured by HPLC, and of tacrolimus will be measured. Whole blood samples (2 ml aliquots) will be taken at the following time points after administration of the medication (time 0): 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 hours. Two weeks subsequently, the patient will receive orally extended release tacrolimus OD 6 mg and mycophenolate mofetil 1000 mg, following the same time protocol for pharmacokinetic analysis.

Data analysis:

This is a prospective study comparing pre-bariatric surgery pharmacokinetics with post-bariatric surgery ones. Each patient will serve as an internal control. The levels of plasma MPA $AUC_{0\text{-}24\ hours}$ and tacrolimus $AUC_{0\text{-}24\ hours}$ will be evaluated at the 2 months, pre-bariatric surgery and at month-12 post-bariatric surgery to determine if there is any significant difference that results from the bariatric surgery. Comparisons will also be made for the volume of distribution and C_{max}.

All patients will complete the SF-36 quality of life questionnaire every three months. Any trends in the score will be compared between baseline (pre-bariatric surgery) and month 3, baseline and month 6, baseline and month 9, and baseline and month 12. The change over time will be calculated on a per patient basis. A clinically significant change is considered to by ≥ 10 points. The incidence of adverse events and serious adverse events will be evaluated every three months for all patients.

The renal function (creatinine clearance by 24h urine collection and with the MDRD formula), if pre-dialysis, will be evaluated at month 6 and month 12 post bariatric surgery for patients in this sub-group and will be compared to baseline numbers.

Number of centers & patients:

This is a single centre study. The clinical assessment and pharmacokinetics will be performed at Hôpital Maisonneuve-Rosemont. The bariatric surgery, including the independent consultation and operation, will be performed at either the Hôpital Sacre-Coeur or the Royal Victoria Hospital.

Population:

The study population will include adult patients (> 18 years) who have stage 4 or 5 chronic renal disease (CrCl < 30 ml/min) who are being considered for possible future kidney transplantation. The study inclusion criteria are an indication for laparoscopic sleeve gastrectomy (BMI > 40 kg/m^2, or BMI > 35 with at least one co-morbidity such as hypertension, dyslipidemia or diabetes) as determined independently by the bariatric surgeon.

The exclusion criteria will include medically unfit for surgical intervention, previous gastric or intestinal surgery, pregnancy and a known intolerance to tacrolimus or mycophenolic acid.

Study duration:

The planned study duration is 3 years.

The planned first patient first visit is for June 2013.

The planned last patient last visit is for May 2015 (based on a 24 month planned recruitment period).

Evaluation criteria:

<u>Safety:</u>

During the pharmacokinetic testing, patients will be monitored for symptoms of intolerance due to the test drugs, tacrolimus and mycophenolic acid. The list of possible adverse events includes anaphylaxis (rare but previously described) and gastrointestinal symptoms, such as nausea, vomiting, diarrhea and cramps. It is anticipated that the GI symptoms will be uncommon and mild due to the short exposure to the drugs. Risks associated with the long-term exposure to tacrolimus and its different formulations, such as hypertension, malignancy, infection, renal toxicity, neurotoxicity and diabetes mellitus will be negligible. If patients are found to have active upper gastrointestinal symptoms, active peptic ulcer disease will be assessed with an oro-gastro-duodendoscopy to avoid exacerbation from mycophenolate mofetil.

Evaluation schedule:

Time of visit	**Day 0**	**q3months pre-bariatric surgery**	**2-months pre-bariatric surgery**	**3-months post-bariatric surgery**	**6-months post-bariatric surgery**	**9 months post-bariatric surgery**	**12-months post-bariatric surgery**
Informed consent	X						
Inclusion/exclusion criteria	X						
Interview and Physical examination (vital signs, height, weight and abdominal circumference)	X	X	X	X	X	X	X
Pregnancy test	X		X				X
SF-36 questionnaire	X	X	X	X	X	X	X
24h creatinine clearance (pre-dialysis only)			X				X
Urine prot/creat (predialysis only)	X	X	X	X	X	X	X
Complete blood work-up*			X				X
MPA AUC $_{0\text{-}24h}$			X				X
Tac AUC $_{0\text{-}24h}$			X				X
Review of concomittant medication	X	X	X	X	X	X	X

* Hematology (WBC, hemoglobin, platelets); renal function (serum creatinine, urea, sodium, potassium, chloride, magnesium, calcium, phosphate and bicarbonate); liver function (AST, ALT, alkaline phosphatase, bilirubin, albumin and pre-albumin); lipid profile (cholesterol, HDL, LDL)

coagulation profile (prothrombin time, INR); nutritional profile (ferritin, vitamin B1, B6, folic acid and zinc); endocrinology (calcium, 25-OH-vitamin D, parathyroid hormone (PTH), TSH, uric acid, glucose and HbA1C)

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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 Institutional Review Board/Independent Ethics Committee/Research Ethics Board approval and the written informed consent of the patient.

1 Introduction

Morbid obesity is an epidemic in Canada and particularly, in the chronic kidney disease patient. According the National Institute of Health, a BMI greater than 30 kg/m^2 is considered obese and

greater than 40 kg/m^2 is morbid obesity. Morbid obesity is a risk factor for developing kidney disease with a 3-fold risk at a BMI > 30 kg/m^2, and 7-fold when > 40 kg/m^2 (1, 2). Amongst kidney transplant recipients, obesity is associated with a longer operative time and length of stay post-operatively (3) (Olarte, Singh), increased risk of post-operative complications (4), including surgical site infections (Johnson, Singh), lymphoceles and hematomas (Singh). Clearly, morbid obesity makes the operation more technically difficult. Obesity also is a risk factor for poor graft function immediately after transplantation. A BMI > 30 kg/m^2 in a single centre study demonstrated worse renal function from 6 months until 3 years with increased episodes of acute rejection (3, 4) delayed graft function (3) and increased metabolic and cardiac complications (4). A national database study of the United States Renal Disease Study demonstrated that amongst 51 927 patients, those with a BMI > 36 kg/m^2 had an increased risk of delayed graft function, increased risk of graft loss and increased risk of death with a functioning graft (5). This same study demonstrated increased risk of developing or worsening hypertension, diabetes, dyslipidemia, proteinuria and glomerulonephritis. Other database studies have demonstrated a decreased graft survival for obese patients (3, 6) and patient survival after transplantation (6). The most telling study demonstrated that for obese patients there was still a survival benefit for transplantation versus remaining on dialysis, however amongst morbidly obese patients (>40 kg/m^2) this was lost (7).

Almost all transplant centres in Canada have imposed a maximum limit for the body mass index (BMI) for acceptance to the waiting list. However, at the same time, the ability of this patient population to lose the excess weight through nutritional modifications and physical exercise is severely limited due to the constraints of renal disease such as its dietary limitations, and the chronic malaise and fatigue of dialysis. If these patients are denied transplantation due to the disease of morbid obesity, a reasonable and effective treatment plan must be offered to provide any hope of life-saving kidney transplantation.

Bariatric surgery has become one of the most commonly performed operations in North America. There are two mechanisms through which the operation helps patients lose excess weight. A restrictive component decreases the volume of the stomach limiting physically the amount of food a patient can eat during a meal. A malabsorptive component bypasses functional intestine decreasing the absorptive capacity of the intestines and the amount of calories a patient can digest and retain.

A few small retrospective case series have reported the efficacy of bariatric surgery in the pre- and post-transplant populations. Scarce data have been reported on the effect of bariatric surgery on

immunosuppressive medication, in particular, the bioavailability. Prospective data is required to define the safety, efficacy and role of bariatric surgery in the management of morbidly obese kidney transplant candidates.

Currently, sleeve gastrectomy represents a restrictive operation that avoids the foreign body of a gastric band and the malabsorption of operations such as Roux-en-Y gastric bypass or duodenal switch. Performed laparoscopically, it can provide effective weight loss in the moderate category of morbid obesity (BMI: 40 - 50 kg/m^2) and may potentially have little impact on the pharmacokinetics of the immunosuppressive medications, in comparison to the malabsorptive procedures. The study will focus on pre-transplant patients to address the obesity prior to the transplantation operation, in an effort to reduce the risks of peri-operative complications and to minimize the potential risk to the graft, if indeed there is a change in the pharmacokinetics of the immunosuppressive medications.

A standard regimen of immunosuppression usually includes tacrolimus, mycophenolate mofetil (MMF) and prednisone. Though practical dosing of tacrolimus is routinely gauged by trough levels of the twice-a-day dosing, pharmacokinetics studies including an AUC 0-12 hours and a C_{max} are of particular interest in judging the pharmacokinetic and adverse effect profile. With regards to MMF, the measurement of plasma MPA AUC 0-12 hours is the most accurate way to determine MPA exposure in renal transplant patients. An AUC in the range of 30 to 60 μg*h/mL has been described as the target to maximize immunosuppression while minimizing MPA-related side effects. More recently, extended release formulations of tacrolimus and an enteric-coated version of mycophenolate acid have been used clinically to provide more stable absorption curves and fewer adverse events.

2 Study objectives

Primary objectives:

1- Evaluate the change in the pharmacokinetics of oral immunosuppressive medications at baseline versus month 12 post-sleeve gastrectomy.

2- Evaluate the degree of weight loss attained through bariatric surgery in the chronic renal failure patient.

3- Evaluate the change in general quality of life score, SF-36, at baseline pre-bariatric surgery versus month 12 post-bariatric surgery.

Secondary objectives:

1. To evaluate changes to residual renal function in the pre-dialysis renal transplant candidate at baseline versus month 12 post-bariatric surgery.
2. To evaluate improvements in co-morbidities including, hypertension, hyperlipidemia and diabetes mellitus, as measured by the number and dose of medications required and the Hb_{A1C}.
3. The incidence of adverse events and serious adverse events at month 1, month 6 and month 12, post-bariatric surgery will be evaluated, in particular, the development of malnutrition, infectious post-operative complications, delays in the time to wait listing and dysphagia.
4. The peri-operative characteristics of the bariatric surgery will also be evaluated including; blood loss, operative time, length of stay, wound complications and dysphagia.
5. The incidence of acute rejection, peri-transplantation complications and delayed graft function will be evaluated at 12 months after (eventual) kidney transplantation.

3 Investigational plan

3.1 Overall study design

The observational study will be divided into two stages: initially all patients will be enrolled in the *Medical Management* stage. During this period the patients will use dietary modifications and physical exercise to lose the excess weight and have regular follow-up for monitoring of their obesity. If these measures fail to help the patient attain the target weight in a reasonable time period, a consultation with a bariatric surgeon will be made.

The *Bariatric Surgery* stage will begin once the patient has consented to and has been accepted for a laparoscopic sleeve gastrectomy and has also consented to enter the pharmacokinetic studies. The number of patients in this group will be twenty and each patient will act as an internal control. The pharmacokinetics of standard immunosuppressive agents will be studied and compared between the pre-bariatric and the post-bariatric times. The medications studied will include tacrolimus, regular and the prolonged-release formulation, and mycophenolic acid, the regular and enteric-coated formulation. As such there will be two days of pharmacokinetic studies about two months before the bariatric surgery and an identical set, one year after the bariatric surgery.

The *Bariatric Surgery* stage begins two months prior to the operation, then regularly every three months afterwards until one year, at which point the second set of pharmacokinetics will be performed and compared to the pre-operative tests.

3.2 Study visits

Initial Visit (Day 1)

At the first visit of the *Medical Management* stage, the eligibility will be confirmed and the project will be explained. Once consent has been obtained to participate in the study, an interview with the doctor will be done with a complete history and physical examination, including blood pressure, height, weight, heart rate and waist circumference. A consultation with a nutritionist will be arranged to identify a dietary plan to reduce calories while respecting the limits of chronic renal disease, diabetes, dyslipidemia and hypertension; and maintaining daily nutritional requirements. A target weight will be identified based on a minimum weight loss of 2 kg/month. Advice on physical exercise will be given to adapt for medical and personal situation of each patient.

Complete blood work tests and urine analysis will be done to establish the nutritional profile, residual kidney function (if pre-dialysis) and, the liver and thyroid functions. All woman of childbearing age will also have a pregnancy test done. All current medications will be documented and the patient will complete a quality of life questionnaire, the SF-36 short form.

Regular Study Visits

These visits will take place every three months during the *Medical Management* stage. Progress in the weight loss will be reviewed and a physical exam, including blood pressure, waist circumference and weight, focused on the morbid obesity, will be done. The SF-36 questionnaire will also be completed along with a review of any changes to the patient's medications and co-morbid conditions. Any difficulties in the domain of the weight loss will also be discussed. For pre-dialysis patients, a blood sample will be drawn for serum creatinine and GFR (MDRD formula).

During the *Medical Management* stage, if patient fails to lose weight at a reasonable rate (a minimum loss of 2 kg/ month) after 6 months, a consultation with a surgeon specializing in obesity or bariatric surgery will be made. This evaluation will take place at either the l'Hôpital Sacré-Cœur or the Royal Victoria Hospital, where these types of specialized surgeries are practiced in addition to having access to hemodialysis and Nephrology services. The surgeon will determine whether an operation for obesity

is indicated. If the decision is taken to proceed to bariatric surgery, the patient will enter the Bariatric Surgery group of the study. The nurse co-ordinator will arrange with the patient two dates when the pharmacokinetics will be performed about two months prior to the bariatric surgery.

If it is determined that a bariatric surgery is not indicated or is too risky, the patient will continue in the Medical Management stage of the study. A weight loss program will be continued primarily based on dietary changes and physical exercise.

3.2.1 Pharmacokinetic studies

Two months prior to the scheduled bariatric surgery patients will be scheduled for two days of pharmacokinetic testing, about one week apart. In addition to a protocol of a regular study visit, a pregnancy test will be performed, if applicable and a 24-hour urine collection, if pre-dialysis to quantify proteinuria and creatinine clearance.

A fasting control blood sample will be taken at 08:00 for tacrolimus and MPA levels. At the first visit the patient will be given tacrolimus (Prograf) 3 mg and Mycophenolate sodium (Myfortic) 720 mg (time 0). Over the next twelve hours, ten blood samples taken at specific time points (0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours) after the medications were taken. A final blood sample will be taken the following morning at 24 hours. In total, eleven samples (44 ml) of blood will be taken. To simplify the blood sampling a temporary antecubital i.v. catheter will be installed. During the day at the hospital, the patient will also be provided with three standardized meals after the 1, 4 and 8 hour time points. At the second visit, the protocol will be repeated with prolonged-release tacrolimus (Advagraft) 6 mg and Mycophenolate Mofetil (Cellcept) 1000 mg.

One year after the bariatric surgery, a second set of pharmacokinetic studies will be performed.

The $AUC_{0\text{-}24h}$ will be calculated using the using the linear trapezoidal method.

Surveillance post-bariatric surgery

Patients undergo a regular study visit every three months until the final two pharmacokinetic studies at one year post-bariatric surgery. The surveillance visits will include an update of the patient's comorbidities, a physical examination including vital signs (blood pressure) and weight assessment. Furthermore, any complications resulting from the bariatric surgery will be noted. For pre-dialysis patients, a blood sample will be drawn for serum creatinine and GFR (MDRD formula) and a urine

sample will be used to quantify proteinuria (urine protein/creatinine ratio). Quality of life will also be assessed using the SF-36 short form. At one year, the patients will have the final two days of pharmacokinetic studies performed as previously described.

3.2 Study population

The study will enroll 20 patients into the *Bariatric Surgery* stage.

Inclusion criteria

1. Chronic kidney disease (stage IV or V)
2. Willing to provide written informed consent
3. Women of childbearing age must have a negative pregnancy test and use a medically acceptable method of contraception throughout the treatment period;
4. Over 18 years of age.

Exclusion criteria

1. Previous gastric, extensive (>50%) small bowel surgery or bariatric surgery, including gastric band, gastric balloon.
2. Known history of gastro-intestinal disease that may affect intestinal absorption
3. Female patients who are pregnant or lactating;
4. Active bacterial, viral or fungal infection;
5. Known sensitivity to the study drugs;
6. Receiving any medications or natural products or herbal remedies that are intended to help a patient lose weight.
7. Any contra-indications to bariatric surgery.

3.3 Treatments

Pharmacokinetic analysis of standard immunosuppressive medications

Mycophenolate mofetil and mycophenolate sodium enteric-coated tablets (MYFORTIC*) are two different formulations to deliver the active moiety mycophenolic acid (MPA), an immunosuppressive agent. This agent is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants.

Tacrolimus and extended-release capsules of tacrolimus (Advagraf) are two formulations of a standard immunosuppressive medication. It is also indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants.

Bariatric surgery

Sleeve gastrectomy is a restrictive gastric operation that is used to help morbidly obese patients lose weight. Bariatric surgery is indicated for morbid obesity for any patient with a BMI greater than 40 kg/m^2 or; with a BMI greater than 35 kg/m^2 and co-morbid diseases such as hypertension, diabetes or dyslipidemia.

Table 1.

Time of visit	*Day 0*	*q3m pre-bariatric surgery*	*2-mo pre-bariatric surgery*	*3-mo post-bariatric surgery*	*6-mo post-bariatric surgery*	*9 mo post-bariatric surgery*	*12-mo post-bariatric surgery*
Informed consent	X						
Inclusion/exclusion criteria	X						
Interview and Physical examination (vital signs, height, weight and abdominal circumference)	X	X	X	X	X	X	X
Pregnancy test	X		X				X
SF-36 questionnaire	X	X	X	X	X	X	X
24h creatinine clearance (pre-dialysis only)		X					X
Urine proteinuria/creatinine (pre-dialysis only)	X	X	X	X	X	X	X
Complete blood work-up*			X		X		X
MPA AUC $_{0\text{-}24h}$			X				X
Tacrolimus AUC $_{0\text{-}24h}$			X				X
Review of current medication	X	X	X	X	X	X	X

AE's and SAE's	X	X	X	X	X	X	X

Laboratory tests

All routine tests will be performed at Hôpital Maisonneuve-Rosemont. For all patients, blood will be drawn for hematology (Hemoglobin, WBC, differential, platelet count) and to measure serum creatinine and urea.

All female patients will undergo a urine pregnancy test at the start of the study and prior to each pharmacokinetic study.

The pharmacokinetic analysis will comprise: Absolute Bioavailability (%), Cmax (ng/mL), Tmax (hr), $AUC_{0\text{-}24\ hrs}$ (ng•hr/mL), V (L/kg), Clearance (L/hr/kg), $t_{1/2}$ (hr), MPA $AUC_{0\text{-}24\ hours}$ and tacrolimus $AUC_{0\text{-}24\ hours}$.

3.6 Safety assessments

The incidence of adverse events and serious adverse events one week after the pharmacokinetic analysis and every three months after bariatric surgery will be evaluated for all patients (secondary objective).

Laboratory evaluations will include hematology (hemoglobin, WBC, differential, platelet count), serum creatinine and urea.

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, as described in the study manual.

An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy). Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

4 Data management and statistical methods

Data analysis

This study, and its exploratory analyses, will use descriptive statistics. The data will be summarized with respect to demographic and baseline characteristics and efficacy and safety observations. Data will be analysed using the pre- and post-bariatric surgery values as a paired cohort, comparing pre- and post-bariatric surgery data.

There will be comparison of the SF-36 score between baseline and month 3, baseline and month 6, baseline and month 9, and baseline and month12.

Sample size

This not a powered trial; no formal sample size has been calculated. A total of 20 patients will be enrolled to study the pharmacokinetics in the chronic renal failure population before and after bariatric surgery.

6 Signatures and addresses

Signature of Investigator(s) and Study Personnel

signature

25 avril 2013
date

Dr. Gabriel Chan

Hôpital Maisonneuve-Rosemont

Montreal QC

Appendix 1. SF-36 quality of life questionnaire.

References

1. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med. 2006;144(1):21-8. Epub 2006/01/04.

2. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyren O. Obesity and risk for chronic renal failure. J Am Soc Nephrol. 2006;17(6):1695-702. Epub 2006/04/28.

3. Gore JL, Pham PT, Danovitch GM, Wilkinson AH, Rosenthal JT, Lipshutz GS, et al. Obesity and outcome following renal transplantation. Am J Transplant. 2006;6(2):357-63. Epub 2006/01/24.

4. Ditonno P, Lucarelli G, Impedovo SV, Spilotros M, Grandaliano G, Selvaggi FP, et al. Obesity in kidney transplantation affects renal function but not graft and patient survival. Transplant Proc. 2011;43(1):367-72. Epub 2011/02/22.

5. Meier-Kriesche HU, Arndorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. Transplantation. 2002;73(1):70-4. Epub 2002/01/17.

6. Aalten J, Christiaans MH, de Fijter H, Hene R, van der Heijde JH, Roodnat J, et al. The influence of obesity on short- and long-term graft and patient survival after renal transplantation. Transpl Int. 2006;19(11):901-7. Epub 2006/10/05.

7. Glanton CW, Kao TC, Cruess D, Agodoa LY, Abbott KC. Impact of renal transplantation on survival in end-stage renal disease patients with elevated body mass index. Kidney Int. 2003;63(2):647-53. Epub 2003/03/13.

Date: ☐☐-☐☐☐-☐☐☐☐ -☐☐☐

Patient Rand. No.

Visit month: ☐☐ (please use 0R for randomization)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Patient Rand. No.

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a kilometre	☐ 1	☐ 2	☐ 3
h Walking several hundred metres	☐ 1	☐ 2	☐ 3
i Walking one hundred metres	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much bodily pain have you had during the past 4 weeks?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Patient Rand. No.

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Patient Rand. No.

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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