



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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INFORMATION AND CONSENT FORM

STUDY 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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Funding partners: Astellas Pharma Canada Inc.
Canadian Association of General Surgery

INTRODUCTION

Prior to giving your consent to participate in this clinical study, please take the time to carefully read the description of the study, including the goal of this research, the possible risks, advantages and other information. You are welcome to ask any questions to the physician, nurse or any other member of the research team. You may also take a copy of this description home with you to think about and discuss it with your family and friends before taking any decision.

GOAL OF THE STUDY

You have been invited to take part in this research study because you need to lose weight prior to becoming a kidney transplant candidate. If you are unable to lose the extra weight through the regular weight loss program, you will be assessed by a surgeon who specializes in obesity surgery or bariatric surgery. The bariatric surgeon will determine whether a weight loss operation is possible. The operation used in this study will be a *Laparoscopic Sleeve Gastrectomy*, which through small keyholes in your skin, instead of a long incision will reduce the size of the stomach to a narrow tube. After the surgery, you will lose weight because you will only be able to eat very small meals.

In order to have a kidney transplant, you will need to take pills for the rest of your life to prevent your body from rejecting the new organ. Since any operation on the stomach can affect the absorption of medications, we wish to study and compare the levels the anti-rejection drugs before and after the obesity surgery. *Pharmacokinetics* is the study of the time necessary to absorb a drug, the time of its action, where it goes in your body and the time required before your body eliminates it.

All the anti-rejection drugs studied in this project are approved for use in Canada and are actually used every day in the transplant centres of Canada and the world.

The goal of this observational study will be to evaluate at one year after the bariatric surgery,

1. The change in absorption (pharmacokinetics) of anti-rejection drugs due to the weight loss surgery.
2. The weight loss achieved through sleeve gastrectomy in patients with kidney disease
3. The change in quality of life due to the weight loss and surgery

This study will include 20 participants and will take place at the Hôpital Maisonneuve Rosemont.

STUDY CONDUCT

This observational study will last until twelve months after the obesity surgery. If you agree to participate, you will have to come to the hospital every three months for the evaluation of your weight loss and undergo a physical examination. We will also discuss any changes to your other medical problems and discuss any symptoms that you may be feeling. We will also update the list of your medications. In addition, you will complete a general questionnaire regarding your quality of life, the SF-36 at each hospital visit you have. This questionnaire is used to determine how you are feeling and your general health.

These questions will take about 15 to 20 minutes of your time. You are always free to skip any questions that make you feel uncomfortable. As much as possible, your visits for this study will be scheduled on the same day as any of your routine consultations at the hospital.

Visit 1

At the initial visit for the study, after your eligibility has been confirmed and you consent to participate in the study, an interview with the doctor will be done to review your complete medical history followed by a complete physical examination. A consultation with a nutritionist will also be arranged to measure your body mass index and establish a dietary plan to reduce calories while respecting the limits of chronic renal disease, diabetes, dyslipidemia and hypertension; and maintaining your nutritional needs. You will be given a target weight to attain and advice on physical exercise, all adapted for your medical and personal situation.

Blood tests and urinal analysis will be done to establish your nutritional profile, your residual kidney function (if you are not on dialysis yet) and your liver function. If you are a woman of childbearing age, a pregnancy test will be done.

We will also discuss any worries or symptoms you may be feeling or having, and which medications you are currently taking.

Routine Study Visits (every three months)

At each of these visits, you will undergo a complete physical examination, including your blood pressure, height, weight and calculation of your BMI. You will also complete a questionnaire concerning quality of life and verify whether there have been any changes to your regular medications. We will discuss with you any difficulties you may have been having with the progress, goals or advice regarding your weight loss program.

During this Observational Stage, if you gain weight or fail 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 requested. This evaluation will take place at either the l'Hôpital Sacre-Cœur or the Royal Victoria Hospital, where these types of specialized surgeries are practiced in Montreal, Quebec. The surgeon will determine whether an operation for obesity is possible and will benefit you in your overall health condition. If the decision is taken to proceed to bariatric surgery, you will enter the Bariatric Surgery phase of the study. During the last study visit, about two months before the bariatric surgery, we will perform pharmacokinetic studies of the absorption of anti-rejection medications. In all these supplemental visits will require your presence at the hospital for two 12-hour days within a week's time.

If it is determined that a bariatric surgery is not necessary or too risky for you, or if your weight loss is equal or more than 2 kg/month, you will continue in the Observational phase of the study. You will continue the weight loss program with dietary changes and physical exercise.

Supplemental Visits for Pharmacokinetics (2 months prior to bariatric surgery)

At a supplemental visit, you will have a pregnancy test (if applicable), a 24-hour urine collection and the pharmacokinetic test, in addition to the other elements of a routine study visit.

Pharmacokinetic tests

Once the decision has been made to proceed with the bariatric surgery, you will be asked to come to the hospital for the entire day on four separate occasions. Two visits will occur before the bariatric surgery and two others one year after the bariatric surgery.

At the beginning of each of these visits, you will take two different anti-rejection medications. The first time you will take one pill of Tacrolimus (Prograf) 3 mg in the morning and 3 mg on the evening at 12h apart, and Mycophenolate sodium (Myfortic) 720 mg in the morning and 720 mg on the evening at 12h apart ; and at the second visit, you will take 1 dose of Tacrolimus long-acting (Advagraft) 6 mg once in the morning and

Mycophenolate Mofetil (Cellcept) 1000 mg twice at 12h apart. Subsequently over the next twelve hours, you will have ten blood samples taken at specific time intervals after the medications were taken. A final blood sample will be taken the following morning 24 hours after taking the medications. In total, 44 ml of blood will be taken. To simplify the blood sampling a temporary i.v. catheter will be installed in your elbow. During the day, you will also be provided with three standardized meals.

First two sets of visits will be done one week apart about two months before the surgery. The second set of visits will then be performed about one year after the bariatric surgery. During the year after the bariatric surgery, you will continue to have visits every three months to monitor your weight loss, health and kidney function, if applicable.

RISKS AND INCOMFORTS

Risks related to study medications

It is possible that you may experience side effects from the study medication. The frequent ones are gastrointestinal symptoms such as diarrhoea, nausea, vomiting, abdominal cramps and rarely, allergic reactions. However, as you will take the study medications for a very short period of time (24 hours), we predict that the side effects will be mild and rare.

Risks related to study procedures

Risks related to blood samples are local pain, ecchymosis, swelling, and rarely, infection, clotting or vein inflammation.

You will be closely followed to cure rapidly any problem or side effect

There could be other side effects that are currently unforeseeable. It is therefore important that you report the occurrence of any unusual symptoms to your study doctor/nurse immediately

Bariatric surgery risks will be explained to you by the surgeon at your evaluation.

Risks related to pregnancy / Contraceptives

Taking part in this study may imply currently known or unknown risks for pregnant women, embryos, fetuses or breastfeed infants. That is why pregnant or breastfeeding women may not participate in this study.

Women who may become pregnant shall undergo a pregnancy test before they take part in this study. Pregnancy should be avoided because the adverse effects of Advagraf on fetuses are unknown. Individual studies conducted on tacrolimus showed toxicity to the fetuses and the FDA (Food and Drug Administration) added a warning list for the drugs Cellcept and Myfortic based on the fact they cause miscarriages and damages to the fetus including congenital abnormality to offsprings of pregnant women taking the treatment.

Men and women participating in this study, who are sexually active shall use a medically reliable contraceptive method for the duration of their participation in this study.

The study doctor or staff will verify your contraceptive method to ensure it is medically reliable.

POSSIBLE BENEFITS

Taking part in this study does not such benefit your health but it would be interesting to see your organism reaction with immunosuppressor drugs. However, your participation in this study may contribute to obtain data which will be useful to evaluate the security and efficacy of bariatric surgery.

FINANCIAL COMPENSATION

You will not receive any financial compensation for your participation in this study. However, you will be reimbursed for transportation and/or parking fees upon presentation of your receipt for additional visits and days allowed to pharmacokinetic study.

INDEMNIFICATION

If you are injured as a result of being given a drug or any other procedure related to this research project, you will receive all care and services required by your health condition at no cost to you.

By agreeing to participate in this project, you do not give up any of your rights or release the investigators, the sponsor, or the facility from their civil and professional responsibility.

VOLUNTARY PARTICIPATION / RIGHT TO WITHDRAW FROM THE STUDY

Your participation in this research project is voluntary. Therefore, you are free to refuse to participate. You may also withdraw from the project at any time, without having to justify your decision (unless you present some adverse effects you have to report quickly) by informing the project investigator or a project staff member of your decision.

Your decision to not participate in the research project or to withdraw from it will neither affect the care and services quality to which you are entitled nor your relationship with the project investigator and the other staff.

The research project investigator, and the Institutional Review Board of Maisonneuve-Rosemont Hospital may end your participation without your consent if new discoveries or information indicates that your participation in the study is no longer in your interest, if you do not follow the research project instructions, or if there are administrative reasons to cancel the project. If your transplantation is performed and your immunosuppressive medication doesn't include tacrolimus, mycophenolate or other formulations, you may also be withdrawn from the study.

If you withdraw or are withdrawn from the project, the medical information already obtained as part of the project will be kept and used as long as necessary to ensure your safety as well as other participants' safety and also to meet regulatory requirements. Furthermore, we will ask you to follow some procedures in the final visit, such as laboratory analysis and a physical examination. However, no new data will be collected from your records.

Any new information that may affect your decision to continue to take part in this study will be immediately communicated to you both verbally and in writing.

CONFIDENTIALITY

While you are participating in this project, the responsible investigator and staff will collect and record information about you in a research record. Only information necessary to meet the scientific objectives of the project will be collected.

This information may include your medical chart history data about your past and present health condition, your life habits as well as tests, examination and procedure results that will be gathered about you during this research project. Your chart could also include other information such as your name, date of birth, your gender and your ethnicity.

All information collected will remain strictly confidential to the extent provided by law. To protect your identity and the confidentiality of the information, you will be identified only by a code number. The code key linking your name to your research record will be kept by the responsible investigator.

The responsible investigator and staff will send the data about you to the sponsor or its representatives. The data does not include your name or address.

The data will be used by the sponsor only for research purposes aimed to answer the scientific objectives of the project described in this information and consent form.

The blood samples will be analyzed at Hôpital Maisonneuve-Rosemont Laboratory. The analysis results will be filled in your medical chart, because they will be useful to your follow-up. No genetic analysis or banked will be performed.

The data, by itself or combined with data from other projects, may be shared with regulatory agencies in Canada or other countries or with business partners of the sponsor. Sending of information implies that your data could be sent to countries other than Canada. The sponsor, however, will respect the confidentiality regulations in effect in Quebec and Canada in all countries. The data will be stored in a secure location for 25 years by the responsible investigator and the sponsor.

The project data could also be used to obtain approval to market the study drug from authorized regulatory agencies. It could also be used for other data analyses related to the project or for the development of future research projects.

The data may be published in specialized journals or be the subject of scientific discussions, but it will not be possible to identify you. For purposes of monitoring and verification, your research record and your medical records may be reviewed by a person appointed by the Institutional Review Board of Maisonneuve-Rosemont Hospital or by the institution, by a person appointed by authorized public agencies, and by representatives of the sponsor. All these people and organizations adhere to a confidentiality policy.

For protection purposes particularly to be able to contact you quickly, your last name, first name, contact information, and the start and end dates of your participation in the project will be stored for one year after the end of the project in a separate record kept by the responsible investigator.

You have the right to review your research record to verify the information collected and to have it corrected if needed as long as the project investigator or the institution has the information. To

maintain the scientific integrity of the study, however, you might not have access to some of the information until your participation has ended.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Upon written request to the study doctor, you may receive the results of this study once it is completed and the results are published.

FUNDING OF THE RESEARCH PROJECT

The investigator and the institution have received financing from Astellas Pharma Canada, Inc. and Canadian Institutes of Health Research in order to conduct this study.

IDENTIFICATION OF CONTACT PERSONS.

If you have any questions or have any problems related to the research project or if you wish to withdraw from it, you can contact the principal investigator of this research project, or someone on the research team, at the following numbers:

(514) 252-3400, poste 6500 (daytime)

or pager: (514) 406-9185 (after working hours)

In the event of an emergency, please contact Dr.Chan, at the following number: (514) 252-3400, poste 4558 or go to the emergency room of the nearest hospital.

For any question concerning your rights as a participant in this research project or if you have any complaints or comments to make, you can contact the service quality and complaints commissioner for the CIUSSS de l'Est-de-l'Île-de-Montréal at (514) 514-3400, extension 3510.

ETHICAL REVIEW OF THIS RESEARCH PROJECT

The Research Ethics Committee of CIUSS de L'Est-de-L'Île-de-Montréal has approved this study and ensures its follow-up. You may reach this committee at (514) 252-3400 extension 5708.

CONSENT AND SIGNATURES

Study title: Prospective, clinical study of the effect of laparoscopic sleeve gastrectomy on the pharmacokinetics of immunosuppressive drugs in the morbidly obese, kidney transplant candidate

I read this Information and Consent Form. I acknowledge that the study has been explained to me, that all my questions have been answered and that I had the necessary time to reach my decision.

I consent to take part in this study at the terms and conditions that were stated. A signed and dated copy of this form will be given to me. Another copy of this form will be filed to my medical record. Consequently, I understand that this information will be available to any person or company to which I give access to my medical records.

I authorize the study doctor to notify my family doctor of my participation in this study:

Yes No

Name and address of my family doctor: _____

Name of participant
(Print)

Signature of participant

Date

Person who has obtained the consent

I have explained to the study participant the terms of the present Information and Consent form and I have answered all his/her questions.

Name of the person
who has obtained the consent

Signature of the person
who has obtained the consent (Print)

Date

Commitment of the Investigator (study doctor)

I attest that I have explained the terms of this information and consent form and all his questions have been answered. The participant has been clearly informed about the possibility to withdraw his participation without any prejudice. I commit myself along with the research team to respect what was agreed, according to the statements on this information and consent form, and I will provide a signed and dated copy to the research participant.

Name of Investigator

Signature of Investigator

Date