UHN Toronto Western Hospital

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

TITLE: A Multisite, Randomized, Double-Blind, Placebo-Controlled 12-Week Study Evaluating the Efficacy, Safety, and Tolerability of Adjunctive Infliximab for the Treatment of Bipolar I/II Depression

PRINCIPAL INVESTIGATOR: Dr. Roger S. McIntyre
(416) 603-5279

Study Contact Number: (416)-603-5133

Introduction

You are being asked to take part in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The following information describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process.

Please ask the study doctor or study team to explain any words you do not understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing this document.

Background

You have been asked to take part in this research study because you are currently suffering form depression and have been diagnosed with bipolar disorder by a health care professional.

Bipolar disorder is usually treated with mood stabilizers and/or antipsychotics. There are many medications that have been shown to help hypo/manic symptoms in individuals with bipolar disorder. The treatment of depression in individuals with bipolar disorder is more difficult and very few medications have proven to be helpful.

This study aims to evaluate the study drug called infliximab as a new treatment option for bipolar depression. Infliximab is currently approved by Health Canada for the treatment of rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriatic arthritis, and plaque psoriasis. In this study, infliximab is an investigational medication. Investigational in this study means that infliximab has not been approved by Health Canada as treatment for bipolar depression. There is evidence that some people with bipolar depression have more inflammation

in the body and this study aims to improve depressive symptoms by reducing inflammation with infliximab.

As part of a sub-study, you will be asked to provide stool samples to examine changes in the bacteria that normally reside in the gut after treatment with infliximab for bipolar depression. The gut is inhabited by millions of bacteria that normally reside in harmony with us and contribute to our health. However, changes that occur amongst the bacteria are now thought to be associated with or even contribute to chronic illnesses. While evidence is still limited in psychiatric illnesses, the available data suggests that this may happen in psychiatric illness as well. Participation in the sub-study is optional and does not affect participation in the main study. You will be asked to indicate your decision at the end of this consent form.

A total of 60 participants will be enrolled in this study; approximately 55 participants will be enrolled from the Mood Disorders Psychopharmacology Unit (MDPU), University Health Network (UHN), at the Toronto Western Hospital.

Purpose

This study is designed to investigate if treatment with intravenous infliximab in addition to your usual treatment will help your mood, your cognition and your quality of life. If it is found that the treatment helps, then it could be a new treatment for bipolar depression.

You should not be enrolled in this study if you have a history of severe infections including severe sepsis, abscesses, tuberculosis, viral hepatitis and HIV because the study drug may activate these infection.

As part of a sub-study, you will be asked to provide stool samples for the investigation of changes in gut bacteria after treatment with infliximab for bipolar depression.

Study Design

This study compares the study drug infliximab with a placebo. A placebo looks just like infliximab but contains no active medication. Whether you get the study drug or the placebo will be decided randomly (by chance) like flipping a coin or rolling dice. The number of people getting infliximab will be 15 and the number getting placebo will be 15, approximately. This study will be double-blinded. This means that neither you nor the study team will know whether you are on infliximab or on placebo until the study is finished. This information can be found out in case of emergency. You will receive infliximab at 3 time points during the study. You will be in this study for 12 weeks after the initiation of treatment. There will be 10 visits during the study. There may be instances when additional visits are required to complete study procedures. Most visits will last for 1.5 hours, though some last longer (please refer to Calendar of Visits).

Study Visits and Procedures

All Visits (Screening Visits to Visit 10)
The following procedures will be performed at all study visits:

- You will be asked about any prescription or non-prescription drugs, herbal or nutritional supplements that you are taking or planning to take. You will also be asked if there have been any changes to your drugs and/or supplements.
- You will be asked about how you have been feeling.
- Your weight and waist circumference will be measured
- Your blood pressure and pulse rate will be measured.
- You will be asked if you have noticed any medical changes.

Visit 1 (Screening Visit)

In addition to the procedures performed for all visits and blood tests, the following will be completed during this visit:

- Your demographic information will be recorded, , including current physical activity levels
- The study team will carry out an interview to confirm your diagnosis of bipolar disorder and your suitability for the study.
- A physical exam will be completed.
- Your height will be measured.
- A pregnancy test (if female) and drug screen will be completed.
- You will be screened for hepatitis and HIV.
- You will also be asked to complete a TB skin test.
- We may contact your doctor for your medical records that are pertinent to your study participation. Your consent will be obtained prior to such contact.

Visits 2, 4, 7

In addition to the procedures performed for all visits and blood tests, the following will be complete during this visit:

- You will receive treatment with either infliximab or placebo. Treatment is administered through infusion into a vein. Infusions will take place at the Toronto Western Hospital. A healthcare professional will oversee the procedure and monitor you for any infusion-related reactions.
- You will provide stool samples (optional).

Visits 2, 4, 10

- Cognitive tests will be completed.

Visits 2-10

–Self-report questionnaires will be completed.

Visits 1, 2, 4, 7, 10

- Blood test may be repeated after visit 1 and before visit 2 upon the doctor's discretion.
- Blood samples will be collected for a routine evaluation (except on visit 2).
- Blood samples will also be collected and stored for the assessment of biomarkers (including on visit 2). Biomarkers are biological markers that may reflect the presence of an illness and/or the severity of the illness.

These are fasting visits. This means that you will be asked to not have food after midnight the night before. This is important to ensure that your blood test results are reflective of your health status. Blood samples will be stored for biomarker analysis. Biomarkers of interest consist of various proteins and mRNA (blueprints that carry instructions for building proteins).

Visits 2, 10

- Two types of medical imaging (i.e., MRI and MRS) will be completed. The MRI will be used to assess the structure and function of your brain whereas the MRS will be used to measure the presence and concentration of various substances that are produced during metabolism in your brain.

At a single time point during the study, a telephone interview will be conducted by highly trained and experienced research staff with the aim to evaluate your history of childhood and adolescent experience. This interview will be audio-recorded. You are not required to answer any question that you are not comfortable answering.

Reminders:

- Please fast for 12 hours before visits 1, 2, 4, 7, and 10.
- Please do not exercise for 48 hours before visits 1, 2, 4, 7, and 10.
- The following medications are prohibited for the duration of your study participation: anakinra, abatacept, other biologics, non-steroidal and steroidal anti-inflammatory medications (Note: prescribed treatment with 81 mg aspirin is permitted).
- Medications that are taken irregularly are restricted. Please consult study doctor and follow advice.

Calendar of Visits

Visit	Interview	Blood Test	Medical Imaging	Treatment	Stool Sample	Time
Visit 1 (Screening)	X	X				3 hours
Visit 2 (Baseline)	X	X	X	X	X	6 hours
Visit 3 (Week 1)	X					1.5 hours
Visit 4 (Week 2)	X	X		X		5 hours
Visit 5 (Week 3)	X					1.5 hours
Visit 6 (Week 4)	X					1.5 hours
Visit 7 (Week 6)	X	X		X	X	4 hours
Visit 8	X					1.5 hours

(Week 8)						
Visit 9 (Week 10)	X					1.5 hours
Visit 10 (Week 12)	X	X	X		X	3.5 hours

Risks Related to Being in the Study

Taking part in this study has risks. Some of these risks we know about. There is also a possibility of risks that we do not know about and have not been seen in humans to date. Please call the study doctor if you have any side effects even if you do not think it has anything to do with this study.

The known risks associated with infliximab infusions are:

Common (20 – 49%):
- Upper respiratory tract infection
- Inflammation of the back throat
- Irritation and inflammation of nasal membrane
- Nausea
- Abdominal pain
- Diarrhea
- Pain
- Headache

Less Common: (1 – 19%)
- Coughing
- Sinusitis
- Bronchitis
- Vomiting
- Indigestion
- Rash
- Itchiness
- Fatigue
- Joint pain
- Back pain
- Muscle pain
- Dizziness
- Fever
- Allergic reactions (immediate or delayed)
- Serious infections including tuberculosis, pneumonia and other infections
- Opportunistic infections such as systemic fungal, viral and bacterial infections

Rare (< 1%):
- Liver injury
- Heart failure

- Low blood counts
- Nervous system disorders
- Tumor, unregulated cell growth or other cancers
- lupus
- psychosis

Treatment with infliximab may also result in reactivation of hepatitis B virus in people who carry this virus.

It is not known if infliximab interferes with vaccinations.

The known risks associated with blood draws/infusions include a slight pain, bruising, and/or inflammation at the insertion site of the needle. Rarely, scarring may occur at the site.

There may be some degree of distress associated with providing stool samples.

There are no known problems associated with the magnetic field used for medical imaging (i.e., MRI and MRS). However, there is a risk if there is any foreign metal object is in your body including a pacemaker, steel plate etc. Please notify the study doctor/study coordinator if this is the case.

Some of the questions asked as part of the study may cause distress or discomfort. You are not required to answer any question that you are not comfortable answering.

Risks Related to Pregnancy

It is not known if the drugs used in this study affect an unborn baby or sperm. You should not become pregnant or father a child while in this study. Men and women who agree to take part in the study must use effective method of birth control during and for 6 months after last study drug infusion.

If you do get pregnant, you should tell the study doctor.

Benefits to Being in the Study

You may or may not receive direct benefit from being in this study. Information learned from this study may help other people with bipolar depression in the future. The research may lead to new advances in understanding, treating, and preventing mood disorders.

Voluntary Participation

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and then change your mind later. You may leave the study at any time without affecting your care.

We will give you new information that is learned during the study that might affect your decision to stay in the study.

Alternatives to Being in the Study Treatments

You do not have to participate to receive treatment for bipolar disorder. You may consider other treatment options including mood stabilizers and/or antipsychotics. There may also be other research studies looking at different treatment for your condition. You may also choose not to have any treatment for your condition. The study doctor will discuss these and other options with you.

Confidentiality

Personal Health Information

If you agree to join this study, the study doctor and his study team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could be used to identify you and includes your:

- Name
- Address
- Date of Birth
- New or existing medical records, which includes types, dates and results of medical tests or procedures.

The information that is collected for the study will be kept in a locked and secure area by the study doctor for 25 years. Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study may also be recorded in your medical record at this hospital.

If you participate in this study, information about you from this research project may be stored in your hospital file and in the UHN computer system. The UHN shares the patient information stored on its computers with other hospitals and health care providers in Ontario so they can access the information if it is needed for your clinical care. The study team can tell you what information about you will be stored electronically and may be shared outside of the UHN. If you have any concerns about this, or have any questions, please contact the UHN Privacy Office at 416-340-4800, x6937 (or by email at privacy@uhn.ca).

All non-identifiable data that is collected as part of this study will be added to the National Institute for Mental Health data repository. The data will be stored in this database indefinitely. This is a requirement by our funding agency (The Stanley Medical Research Institute). Your health information from this research project will be sent to other countries but your identifiers will be removed. They will not be able to identify you.

The following people may come to the hospital to look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines:

- The study sponsor or its representatives/partner companies.
- Representatives of the University Health Network Research Ethics Board.

- Representatives of Health Canada, or other regulatory bodies (groups of people who oversee research studies), outside of Canada, such as the United States Food and Drug Administration

Study Information That Does Not Identify You

Some study information will be sent outside of the hospital to the granting agency. Any information about you that is sent out of the hospital will have a code and will not show your name or address, or any information that directly identifies you.

The Sponsor may use the study information and share it with its partner companies or with national and international regulatory agencies to help answer the study question, to get approval to sell intravenous infliximab, to develop future studies on this product or for research related to this study.

All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. You will not be named in any reports, publications, or presentations that may come from this study.

If you decide to leave the study, the information about you that was collected before you left the study will still be used. No new information will be collected without your permission.

Rights as a Participant

If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form, you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

Costs and Reimbursement

Reimbursement of up to $50 per visit will be offered for food and travel related expenses i.e. parking and public transportation. Receipts are required in order to receive refund.

If you decide to participate in the sub-study, you will receive an additional $10.00 for each visit that requires a stool sample (Visits 2, 4, and 7).

Questions About the Study

If you have any questions, concerns or would like to speak to the study team for any reason, please call: Dr. Roger McIntyre at 416-603-5279 or **Mehala Subramaniapillai** at **416-603-5133 (office)** or **mehala.subram@uhn.ca**. You can also call the 24-Hour emergency study number at (647) 780-9533.

If you have any questions about your rights as a research participant or have concerns about this study, please call the Chair of the University Health Network Research Ethics Board (REB) or the Research Ethics office number at 416-581-7849. The REB is a group of people who oversee the ethical conduct of research studies. The UHN REB is not part of the study team. Everything that you discuss will be kept confidential.

You will be given a signed copy of this consent form.

Consent

This study has been explained to me and any questions I had have been answered. I know that I may leave the study at any time. I agree to the use of my information as described in this form. I agree to take part in this study.

☐ Yes ☐ No I would also like to participate in the optional sub-study

We would like your permission to contact your family physician to obtain additional medical information or to let them know you are participating in this research study. Please check off the appropriate box below indicating your choice to allow us to communicate with your physician or primary care provider.

The study doctor may tell my regular family doctor about my being in this study:

☐ YES ☐ NO

_____	_____	_____
Study Participant's Name	Study Participant's Signature	Date

My signature means that I have explained the study to the participant named above. I have answered all questions.

_____	_____	_____
Name of Person Obtaining Consent	Signature	Date

_____	_____	_____
Name of Principal Investigator	Signature	Date