Informed Consent Form

Phase II Open-Label Trial of Tacrolimus/Methotrexate and Tocilizumab for the Prevention of Acute Graft-Versus-Host Disease After Allogeneic Hematopoietic Stem Cell Transplantation

NCT02206035

28 JAN 2015

Medical College of Wisconsin and Froedtert Hospital
CONSENT TO PARTICIPATE IN RESEARCH

Name of Study Subject: _____

PHASE II OPEN LABEL TRIAL OF TACROLIMUS/METHOTREXATE AND TOCILIZUMAB FOR THE PREVENTION OF ACUTE GRAFT VERSUS HOST DISEASE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

William Drobyski, MD
Froedtert & Medical College of Wisconsin
Division of Hematology and Oncology
9200 W. Wisconsin Avenue
Milwaukee, WI 53226-0509
414-805-6800

You are invited to take part in this research study. This form tells you why this research study is being done, what will happen in the research study, possible risks and benefits to you, your choices, and other important information. If there is anything that you do not understand, please ask questions. Then you can decide if you want to join this study or not.

A1. INTRODUCTION – WHY ARE WE ASKING YOU ABOUT THIS STUDY?

You are being invited to participate in this research study because you are a patient planning to have an allogeneic transplant (commonly known as a bone marrow transplant or peripheral blood stem cells from another person – usually a sibling, but sometimes an unrelated donor) and are at risk of suffering a common problem called acute graft-versus-host disease (aGVHD).

A total of about 35 people are expected to participate in this study all at the Medical College of Wisconsin/Froedtert Hospital.

The Director of the study is William Drobyski, MD in the Department of Medicine. A study team works with Dr. Drobyski. You can ask who these people are.

This study is being funded by a grant called: Kurtis R. Froedtert Clinical Trials Seed Grant and the HMT Immunological Monitoring Shared Resource Funds, which are providing the financial support to Dr. Drobyski to conduct the study. Dr. Drobyski is the sponsor of the study.

A2. DO I HAVE TO BE IN THIS STUDY?

You can decide whether to take part in this study or not. You are free to say yes or no. If you say no, your regular medical care will not change. Even if you join this study, you do not have to stay in it. You may stop at any time.

A research study is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the study procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS RESEARCH STUDY BEING DONE?

Patients who undergo allogeneic transplants are at risk of suffering a common problem called acute graft-versus-host disease (GVHD). Acute GVHD is a complication where the donor cells (graft) received during the transplant attacks and damages the patient's (transplant recipient) tissues. GVHD can cause skin rash, intestinal problems such as diarrhea, nausea, vomiting and decreased liver function or liver failure. These symptoms can range from mild to severe and may be life threatening and may be fatal in some cases.

The purpose of this study is to learn if prescribing Tocilizumab to you starting the day before your transplant will help prevent acute GVHD. We also want to find out whether prescribing Tocilizumab in this way causes any problems (side effects). **Everyone** in this study will receive Tocilizumab. Tocilizumab is currently approved by the Food and Drug Administration to treat severe active rheumatoid arthritis, but it is not approved for use in patients to prevent GVHD. This means that the use of Tocilizumab in this study is considered investigational (or experimental).

There is no universally accepted standard treatment to prevent GVHD, and different transplant centers in the country use a variety of treatments to prevent this complication. In this study you will also be given the standard treatment normally provided at this site to help prevent GVHD in addition to receiving Tocilizumab.

B1. WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

A member of the study staff will discuss with you the requirements for being in this study. First we will need to find out whether you are able to be in the study. You will be asked to give information about your medical history and undergo the exams and tests listed below.

Before you begin the study:

These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Baseline tests include:

- Medical History and a physical examination (including vital signs, height, weight and current medications).
- KPS score-an assessment of your ability to do daily tasks

- Routine blood tests to check your blood counts and organ function
- Routine pre-transplant blood tests
    - A blood or urine test to check for pregnancy for women of childbearing potential
- Electrocardiogram (ECG or EKG), a picture of the electrical action of the heart.
- Echocardiogram (ECHO) (a picture of the heart in motion made using ultrasound or sound waves) or Multi Gated Acquisition (MUGA) scan (a picture of your heart after a small amount of radioactive material is injected into the bloodstream through a vein) to look at your heart function
- Pulmonary Function Test (PFT), which is a breathing test that tells how your lungs are working, measures the amount of air taken into your lungs and exhaled as you breathe.
- Depending on what type of cancer you have you will have the routine tests below to assess your cancer:
    - Bone Marrow aspirate or Biopsy
    - CT and/or PET scans
- Chest x-ray or chest CT

During the study:

If the exams, tests and procedures show that you can be in the study, and you choose to take part by signing this consent, then you will be enrolled in the study.

Conditioning and Your Donor's Collection

Prior to receiving your donor's stem cells you will undergo your transplant conditioning therapy, which includes chemotherapy. Transplant conditioning therapy, is a standard procedure for patients receiving an allogeneic hematopoietic stem cell transplant. Your physician or someone on the transplant team will discuss with you further the details of your conditioning regimen. Your conditioning regimen will include a combination of 2 of the following drugs: Busulfan and either Fludarabine or Cyclophosphamide.

Your donor will donate cells in the way that is determined to be the best by your donor and your physician. A member of the transplant team will discuss the details of the donation process with your donor.

Immunosuppression Therapy

As part of the standard transplant procedure you will also be given drugs to reduce the risk of graft versus host disease (GVHD). There is no standard treatment to prevent GVHD, and different transplant centers in the country use a variety of treatments to prevent this complication. In this study you will be given what is considered the standard treatment for our transplant center to help prevent GVHD. The routine

immunosuppression therapy being used in this study consists of 2 drugs (Tacrolimus and Methorexate).
You will also be given **Tocilizumab**, the drug being researched in this study, as a one-time dose the day before receiving your donor's stem cells in addition to receiving Tacrolimus and Methotrexate.

Transplant

On the day of the transplant the stem cells will be given to you. Your physician or someone on the transplant team will discuss further the details of the transplant with you.

Post-Transplant Follow-up Care, Tests and Procedures

As part of the routine transplant care you will have other tests, procedures and medications that your transplant doctor and team think are necessary to monitor your health. You will be watched for any side effects from the drugs or the transplant itself. You will be given available drugs and/or treatment to lessen any side effects that may occur.

Mandatory Research Samples

As part of this study additional blood will be taken for research at some of your visits (Baseline, days 7, 14, 28, 100,180 and 365). These samples will be used to examine how quickly your immune system regenerates after the transplant. Also, blood samples will be collected to look at the level of inflammation in your body by measuring small proteins which are called cytokines that promote inflammation in the body.

B2. HOW LONG WILL I BE IN THE STUDY?

You will be in this research study for about 1 year after your transplant.

B3. CAN I STOP BEING IN THE STUDY?

You are free to withdraw from the study at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the study doctor.
⇒ The doctor can tell you about the effects of stopping, and you and the doctor can talk about what follow-up care would help you the most.
⇒ You might be asked to come back for one more visit to check your health.

The study doctor may take you out of this study at any time. This would happen if:
- They think it is in your best interest.
- You do not follow the study rules.
- The whole study is stopped.

If this happens, the study doctor will tell you.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE STUDY?

There are risks to taking part in any research study. There is a risk that you may get a drug, drug combination, or dose of a drug that does not help your condition or may make it worse. There also may be problems (side effects) we do not know about yet, from the drug itself, or how it combines with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the study for problems (side effects). **You need to tell the study doctor or a member of the study team immediately if you experience any problems, side effects, or changes in your health.** If you have problems, call Dr. Drobyski immediately at 414-805-6800. In an emergency, call 911.

C2. RISKS OF TOCILIZUMAB

The research drug itself may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away. Many go away soon after you stop taking the drug. Drugs can affect individuals in different ways. Complications of some of the side effects below may lead to life-threatening events possibly death.

More common

- Upper respiratory tract infections
- Inflammation of the nasal passages (nasopharyngitis)
- Headache
- High blood pressure
- Dizziness
- Bronchitis
- Rash
- Mouth sores
- Upper abdominal pain
- Inflammation of the lining of the stomach (gastritis)
- Decreases in white blood cells
- Decreases in platelets
- Increase in liver enzymes in the blood
- Increases in cholesterol

Serious infection

There is a risk of serious infection. Most patients with other diseases who developed these infections were also taking drugs that suppress the immune system such as Methotrexate or corticosteroids. Serious infections leading to hospitalization or death, including tuberculosis, bacterial, invasive fungal, viral and other opportunistic infections have occurred in patients receiving Tocilizumab. Viral reactivation and cases of herpes zoster exacerbation were reported in clinical trials.

Gastrointestinal (GI) Perforations
Events of GI perforation have been reported in clinical trials, primarily as complications of diverticulitis. Please contact your doctor if you have any new symptoms affecting your abdomen.

Hypersensitivity (allergic) and infusion reactions
Sometimes mild to moderate allergic reactions may happen, such as hives, itching and skin rash. Severe or life-threatening allergic reactions, even death, although rare, may also happen. If you do have an allergic reaction, medical treatment will be given to you.

C3. OTHER RISKS OF THIS RESEARCH STUDY

Other procedures and medications that are part of the study also involve some risks:

Side effects of chemotherapy and transplant in general:

- Lower number of blood cells with increased risk of infection, fatigue due to anemia, and increased risk of bleeding (usually temporary but may be permanent)
- Severe and painful mouth sores (mucositis)
- Nausea and vomiting
- Diarrhea
- Hair loss anywhere you have hair (usually temporary, but may be permanent)
- Inability to have children or sterility (usually permanent)
- Poor function of the liver, kidney, lung, brain or any other organ (usually temporary but may be permanent)

Specific side effects of drugs that may be used in the conditioning regimen:

BUSULFAN
Likely Side Effects (May happen in 20% of patients or more)

- Abdominal discomfort
- Constipation
- Diarrhea
- Dizziness
- Fluid retention
- Headache
- Heartburn
- Insomnia
- Lack of appetite
- Mouth sores
- Nausea and vomiting
- Running nose

- Skin rashes
- Irregular or no menstrual cycles
- Tachycardia (rapid heart rate)
- Low blood counts

Less Likely (May happen in less than 20% of patients)

- Cough
- Hepatic Veno-occlusive disease (damage to the liver which can be life-threatening)
- High blood pressure
- High magnesium and phosphorus levels in the blood
- High sugar levels in the blood
- Infertility
- Low blood pressure
- Seizures

Rare (May happen in less than 2% of patients)

- Cataracts
- Lung fibrosis (scarring)

FLUDARABINE

Likely Side Effects (May happen in 20% of patients or more)

- Nausea and vomiting
- Low white blood cell count and increased risk of infection
- Low platelet count and increased risk of bleeding
- Low red blood cell count and increased need for red cell transfusions

Less Likely (May happen in less than 20% of patients)

- Diarrhea
- Loss of appetite
- Fatigue
- Sensitivity to light
- Trouble seeing or problems with your eyes

Rare (May happen in less than 2% of patients)

- Numbness or tingling in your fingers or toes
- Confusion
- Coma
- Lung failure or pneumonia (may be permanent)
- Shortness of breath

CYCLOPHOSPHAMIDE (CYTOXAN)

Likely Side Effects (May happen in 20% of patients or more)

- Damage to male (testes) and female (ovaries) sex glands
- Diarrhea
- Fluid retention
- Hair loss
- Infertility
- Irregular or no menstrual cycles
- Loss of appetite
- Nausea, Vomiting
- Suppression of the immune system
- Low blood counts

Less Likely (May happen in less than 20% of patients)

- Bleeding and/or irritation in the bladder
- Inflammation of the heart muscle (heart failure)
- Shortness of breath

Rare (May happen in less than 2% of patients)

- Allergic reaction
- Lung fibrosis (scarring)
- Serious skin rashes

Side Effects of Other Immunosuppression Medications

TACROLIMIUS

Likely Side Effects (May happen in 20% of patients or more)

- High blood pressure
- Temporary, mild or moderate decrease in kidney function
- Headaches
- Insomnia
- Confusion
- Dizziness
- Nausea and/or vomiting
- Stomach pain or feeling of indigestion
- Loss of body minerals (magnesium, calcium or potassium)
- Tremors (shaking) of arms or legs

- Low blood counts
- Fever and chills
- Fatigue
- Low blood counts
- Abnormal Liver tests
- Infection

Less Likely (May happen in less than 20% of patients)

- Swelling of the hands or feet with a burning sensation
- Elevated blood cholesterol and triglycerides (fats)

Rare (May happen in less than 2% of patients)

- Trouble seeing or problems with your eyes (may be permanent)
- Sensitivity to light
- Muscle cramps
- Numbness and tingling of the hands or feet
- Hard to think
- Seizures (may be life-threatening)
- Kidney damage (may be permanent)

METHOTREXATE

Likely Side Effects (May happen in 20% of patients or more)

- Nausea
- Vomiting
- Loss of appetite
- Mouth Sores

Less Likely (May happen in less than 20% of patients)

- Low white blood cell count and increased risk of infection
- Lower platelet count with increased risk of bleeding
- Diarrhea or loose stools
- Kidney damage (may be permanent)
- Greater risk of sunburn

Rare (May happen in less than 2% of patients)

- Damage to the liver (may be permanent or cause death)
- Allergic inflammation of the lung with fever, cough, and feeling short of breath
- Hair loss

- Skin reactions (rash, itching)
- Feeling dizzy
- Blurred vision
- Hard to think
- Headaches
- Redness of eyes and maybe itching but not serious (conjunctivitis)

Infections

Patients undergoing allogeneic stem cell transplants are at increased risk from developing infections since the transplant conditioning therapy will eliminate your own bone marrow and there will be a period of time when your counts are very low which will put you at risk for infections. Also, since you are receiving stem cells from another person, you have to develop an entirely new immune system which takes time and also increases your risk for infectious complications. If you develop GVHD, there is an increased risk of infection from the GVHD itself and from the treatments that may be used to treat it. Infections may in some cases be bad enough to cause death.

You will need to take several antibiotics to prevent infection. You will also be watched carefully for any infections while you are being treated for GVHD. Tell your doctors promptly if you get a fever, chills, cough or any other symptoms that might be a sign of an infection.

IV Drug administration:

Intravenous administration can cause slight discomfort or bruising at the site where the needle is inserted and may also cause lightheadedness and fainting, infection, and excessive bleeding.

Blood Samples:

The tests done at each visit are standard medical tests. The samples obtained for research purposes will be collected at the same time that you are having routine blood collections to monitor the status of the transplant and your disease. The most unpleasant aspect of this often is having blood samples taken. The risks of taking blood may include fainting, pain and/or bruising. Rarely, these may be a small blood clot or infection at the site of the needle puncture. The blood pressure cuff may also cause discomfort or bruising to the upper arm.

Bone Marrow Biopsy:

You may be asked to undergo a routine bone marrow biopsy at least once during this study depending on your disease. Risks from bone marrow biopsy include pain, infection, and bleeding. Your doctor or other health care provider should discuss the bone marrow biopsy with you at the time the procedure is to be performed.

ECG test:

The ECG test that will be used to monitor your heart rhythm during the study and is a standard medical procedure performed routinely at medical centers. No special risks are identified with this test; however, please ask your doctor if you have any questions about it.

CT or PET scan:

Depending on your disease you may be asked to undergo computerized tomography (CT) scanning during this study as routine care. Risks from this procedure include exposure to radiation and possible reaction to the dye used in the procedure. You will have at least one scan during the screening period and may have additional scans if the investigator feels they are necessary.

C4. REPRODUCTIVE RISKS

Risks to women who could become pregnant

The drug in this study might affect a baby, before or after the baby is born. We do not know if the drug causes harm to a baby, so we do not want anyone who might be pregnant to enter the study. You should not become pregnant or nurse a baby while in this study. You must tell the study doctor right away if you think you are pregnant. You will be asked to have a pregnancy test to be sure you are not pregnant at the start of the study.

Risks of fathering a child

You should not father a baby while taking part in this study because it is unknown if the drug in this study could affect a baby. If your partner is able to become pregnant, one or both of you must use some form of effective birth control. You must tell the study doctor right away if you think your partner is pregnant.

Birth control methods for all subjects

Check with the study doctor about the birth control methods needed for this study and how long to use them. Some methods might not be good enough for this study. If you are having sex that could lead to pregnancy, you should use birth control while you are in this study.

This may include:

- Not having vaginal sex (abstinence)
- Taking birth control pills orally
- Having birth control shots or patches such as Depo-Provera
- Surgical sterilization (hysterectomy or tubal ligation)
- Use of an intrauterine device (IUD)

- Use of diaphragm with contraceptive jelly
- Use of condoms with contraceptive foam
- Use of diaphragm with condoms ("double barrier")
- Limiting sexual activity to a male partner who has had a vasectomy

You should continue using birth control for 3 months after receiving the Tocilizumab.

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

We don't know if this study will help you. We hope the information from this study will help us develop better treatments for prevention of acute GVHD.

D1. ARE THERE ANY COSTS TO BEING IN THE STUDY?

Most of the medical care that you will receive in this study is considered routine care for your condition and would be recommended whether you join the study or not. Costs for routine care will be billed to you or your insurance carrier. Activities / costs that are part of the study will not be billed to you or your insurance company. These are the study drug tocilizumab and processing and shipment of research samples. Some insurers will not pay for drugs, tests or hospitalization that are part of research studies, so check with your insurer before you join this study. If you have questions regarding study costs, please contact Dr. Drobyski.

D2. WILL I BE PAID FOR PARTICIPATING IN THE STUDY?

There is no payment for being in this study

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this study. You are free to say yes or no. If you do not join this study, your doctor can discuss other healthcare choices with you.
Your other choices may include:

- Joining a different research study
- Routine care for this condition or symptoms

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE STUDY?

If we learn any important new information about the drug that might change your mind about being in the study, we will tell you about it right away. You can then decide if you want to stay in the study.

D5. WHAT HAPPENS IF I AM HARMED BECAUSE I TOOK PART IN THE STUDY?

No funds have been set aside to pay any costs if you become ill or are harmed because of this study. If you think that you have become ill or were harmed because of this study, let the study doctors know right away by calling 414-805-6800. By signing this

form, you do not give up your right to seek payment for harm you receive while participating in this study.

If you think that you have become ill or were harmed because of this study, let the study doctors know right away by calling 414-805-6800.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

- If you have more questions about this study at any time, you can call William Drobyski, MD at 414-805-6800.
- If you have questions about your rights as a study participant, want to report any problems or complaints, obtain information about the study, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this study?

To do this research study, we need your permission to collect and use some of your health information, or you cannot be in the study. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the study.

The health information to be collected and used for this study is:

- Hospital/Medical Records
- Physician/Clinical Records
- Lab and/or Pathology Reports
- Radiology Reports
- Biological Samples

E2. Who will see the health information collected for this study?

The only MCW/Froedtert Hospital employees allowed to handle your health information are those on the study team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

The study team may share your information with people who don't work at MCW/Froedtert Hospital because they planned, pay for, or work with us on this study. The federal Privacy Rule may no longer protect your health information once it leaves MCW/Froedtert Hospital. For this study, we plan to share information with those doctors, researchers or government representatives working with us on this study at the institutions or companies listed here:

U.S. Food and Drug Administration, Rockville, MD
Any Independent ethics committee, which approved this study
Any Data Safety Monitoring Board appointed to review this study

Other Regulatory Agencies and/or Their Designated Representatives
Those required by law

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information for a different study without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed, the information might be used or released for other purposes without asking you. Results of the study may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?

One risk of taking part in a research study is that more people will handle your personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the study doctor about whether this could apply to you.

E4. How long will you keep the health information for this study?

If you sign this form, we plan to keep your information without any end-date in case we need to check it again for this study.

E5. Can I cancel my permission to share this health information?

If you change your mind later and do not want us to collect or share your health information, you need to send a letter to:

William Drobyski, MD
Froedtert & Medical College of Wisconsin
Division of Hematology and Oncology
9200 W. Wisconsin Avenue
Milwaukee, WI 53226

The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we may decide that you cannot continue to be part of the study. We may still use the information we have already collected.

F1. FOR MORE INFORMATION ABOUT THE STUDY

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.

You can look up this study by referring to the ClinicalTrials.gov number (NCT02206035) or by asking the study team for a printed copy.

CONSENT TO PARTICIPATE IN THE STUDY

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The study's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the study team use and share the health information and other information gathered for this study.
- I voluntarily agree to participate in this research study. I agree to follow the study procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Subject's Name *please print*	**Subject's Signature**	**Date**
Name of Legally Authorized Representative (if applicable) *please print*	**Signature of Legally Authorized Representative**	**Date**
Name of Witness (if applicable**)** *please print* (for short form consent process, or consent of blind or illiterate subject)	**Signature of Witness**	**Date**
*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

** A member of the study team trained and authorized by the Principal Investigator to act on her/his behalf in obtaining informed consent according to the protocol. In all research study protocols the Principal Investigator is responsible and accountable for the study.*