Informed Consent to Participate in Research

We invite you to participate in this research study. About 180 patients will participate at up to 27 centers around the country. Your study participation will last about 9 months. This is a study for patients who have a new diagnosis of graft-versus-host disease (GVHD) after receiving an allogeneic (donor) stem cell transplant.

GVHD is a medical condition where the donor cells attack and damage your tissues after you have a transplant. GVHD can cause:

- Skin rashes,
- Intestinal problems like feeling sick to your stomach (nausea), throwing up (vomiting), diarrhea, or,
- Liver damage like hepatitis or jaundice.

GVHD can also increase your risk of infection. Sometimes, GVHD can be controlled with treatments that use corticosteroids (like prednisone). More often, patients need long-term drug therapy to control their GVHD symptoms and to suppress the immune system. Long-term drug therapy has risks and side effects. Because of the risks of continued GVHD, new drugs to control GVHD will be tested in this study.

All four drugs being tested in this study are approved by the US Food and Drug Administration (FDA) for treating diseases other than GVHD. This study will test whether these new drugs can help treat GVHD better than the standard therapy of steroids alone. One of the study drugs is given either orally, or if you cannot take pills, then it will be given by IV infusion. The other 3 study drugs are given either by IV or by injection under the skin.

This consent form tells you about the study. The study investigators have found that you are eligible to participate in this study, and this form must be signed before any treatment related to the study is given to you. The doctors in charge of this study (the investigators) or other staff will also discuss this study with you and answer any questions you might have. Before you decide to join this study, please read this information and ask any questions about things you do not understand. Some patients find it helpful to have a family member or friend with them to help ask questions and listen to information.

This study will give more information to doctors about future treatment choices for GVHD. Importantly,

- You will not be paid to be in this study.
- You or your insurance company will pay for all medical bills for your treatment.
- You will not be charged for research tests.
- You will also face the same risks and benefits as any other transplant patient.

Before you decide to join the study, please read the information below. Feel free to ask questions to understand your rights and protections. It is your choice to take part in this study. **You and your doctor will discuss other treatment options if you decide not to be in this study.**

Your Name:_____

Title of Research Study: Initial Systemic Treatment of Acute GVHD: A Phase II Randomized Trial Evaluating Etanercept, Mycophenolate Mofetil (MMF), ONTAK and Pentostatin in addition to Corticosteroids

Principal Investigator: Daniel Weisdorf, M.D., University of Minnesota, MMC 480, Minneapolis, MN 55455, 612-624-3101

Transplant Center Principal Investigator: _____

Study Sponsor: This study is sponsored by the National Institutes of Health (NIH) by providing financial support for this study through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

The drugs in this study were donated by the companies that made them, and these companies also gave some financial support to help pay the costs of this study. These companies did not plan or design this study. In addition, they will not have a part in analyzing the results of this study.

The Purpose of the Study

The study is to test new treatments for acute Graft-versus-Host Disease (GVHD). GVHD is a medical condition where the donor graft attacks and damages your tissues after you have a transplant. If you have limited GVHD of the skin or only GVHD in your upper gastrointestinal (GI) tract, your doctor may decide that you need systemic treatment, though not all patients receive systemic treatment for this type of GVHD. By offering you this study, your doctor recommends that you get additional treatment.

Four new drugs are being tested:

- Etanercept (ENBREL®)
- Mycophenolate Mofetil (MMF) (CellCept®)
- Denileukin Diftitox (ONTAK®)
- Pentostatin (Nipent®)

In this study, use of one of these four drugs, along with prednisone or methylprednisolone, may increase the control of your GVHD. It is uncertain whether use of any of these new drugs will improve control of GVHD.

Each drug will be given along with the standard therapy of prednisone or methylprednisolone which is the usual therapy for acute GVHD. There is no placebo or sugar pill treatment in this trial. Everyone in the study will receive prednisone or methylprednisolone plus one of the four new drugs, unless you are already receiving MMF; then only one of the other 3 drugs will be assigned to you. All patients in the study will be randomly assigned (like flipping a coin) to receive one of the four new study drugs with some statistical adjustment to ensure that about the same number of patients will receive each of the new study drugs.

What will be done if you take part in this study?
In addition to receiving prednisone plus the assigned study drug, for your routine care (outside this study), you will be watched closely for signs and symptoms of:

- GVHD,
- Changes in your blood counts,
- Changes in liver and kidney function, and
- Any signs of infection.

For the study, the GVHD signs and symptoms will be recorded at least once a week for the first 8 weeks. The exam at week 4 and week 8 must be done at the transplant center. Other weekly exams and tests may be done at the transplant center, or at a local doctor's office if your condition improves and it is closer to where you live.

If you are randomly chosen to receive MMF, you will have additional blood samples drawn to study the actions of this drug in your body. You will have 5 mL (about 1 teaspoon) of blood drawn at 4 different times (total of 20 mL) on one day between Days 3 and 7 and again on another day between Days 10 and 14 (for a total of 40 mL). This blood will be drawn from an existing central venous catheter or a temporary peripheral venous catheter.

STUDY DRUGS

What are the possible discomforts and risks?

Infections

Because GVHD is caused by an immune attack on your tissues from the transplanted donor cells, all treatments for GVHD include drugs to suppress (turn off) this immune attack.

The risk of infection is increased in patients with GVHD and those taking immune suppressing corticosteroids like prednisone or methylprednisolone, the standard therapy for GVHD. All four study drugs can also increase your chance of infection. Therefore, you will take several protective antibiotics and be watched carefully for any infections while you are being treated for

GVHD. Tell your doctors promptly if you get a fever, chills, a cough or any other symptoms that might be part of an infection.

Side Effects of Study Drugs

All drugs can have side effects, both the standard therapy (steroids) and the new drugs being tested in this study. Your doctors will watch you carefully for any side effects and will modify your treatment if they develop. Experience with pediatric patients treated with these agents for GVHD is limited.

Etanercept (ENBREL): Etanercept is an anti-inflammatory and immune suppressive drug.

Etanercept can cause certain side effects. Some patients develop redness or soreness at the injection sites. Sometimes headache, dizziness, or rash can occur. A few people develop fever, upper respiratory tract symptoms (like a cold with cough, stuffy nose or sinusitis) and rarely some serious infections have developed in people taking etanercept. Rarely, blood counts can be lowered in people taking etanercept.

In this study, the drug will be given by injection under the skin (subcutaneously) twice weekly for up to four weeks.

Mycophenolate Mofetil (MMF) (CellCept): MMF is a potent immunosuppressive drug that blocks the growth of lymphocytes (immune cells), which can cause GVHD.

MMF can cause certain side effects. Occasionally it can lower the blood counts. More frequently, it can cause nausea, vomiting or diarrhea. Rarely, serious gut injury can occur.

In this study, it is given twice daily as capsules or a liquid. It may be continued for 8-10 weeks or as long as GVHD is active.

Denileukin Diftitox (ONTAK): ONTAK is an immune suppressive drug, but has also been used to treat certain kinds of lymphocyte cancers called T cell lymphomas.

ONTAK can cause certain side effects. Most patients develop a headache, skin rash, fever, chills, muscle aches, and joint aches while the infusion is given or within a day of each infusion. Dyspnea (shortness of breath), chest tightness, and flushing of the skin may occur. Slowing the infusion may minimize these side effects. Occasionally, acute allergic-like reactions with itching, temperature, chills, or a rash can develop. These side effects may be relieved by temporarily stopping and then restarting the infusion and giving medications before the dose of ONTAK like acetaminophen (Tylenol) or diphenhydramine (Benadryl) to try to prevent these reactions.

In a few patients, ONTAK can cause fluid accumulation (edema). This can lead to swelling in the tissues, legs, or rarely fluid in the lungs or low blood pressure. If given in higher doses than in this study, anorexia (loss of appetite), upset stomach with nausea, vomiting or diarrhea can occur. Rarely, liver problems or low blood counts can develop.

In addition, new information has suggested that rarely, vision changes or vision loss can occur in patients treated with ONTAK.

In this study, ONTAK will be given intravenously (over approximately 60 minutes) Days 1, 3, 5 of the first week and repeated in the third week (Days 15, 17, 19) of your treatment.

Pentostatin (Nipent): Pentostatin is an immune suppressive drug that is sometimes used as an anticancer chemotherapy drug as well.

Pentostatin can cause certain side effects. Up to half of the patients develop skin rash, nausea, vomiting, anorexia (loss of appetite), mouth sores, or diarrhea, although these side effects usually occur when patients are given higher dosages of the drug than you will receive on this study. Rarely, patients have kidney trouble. In a few patients treated with higher dosages of pentostatin, low platelet counts, anemia, or increased need for transfusions have developed. Rarely, low white blood cell counts can occur. A small number of patients also develop temporary abnormalities in their liver function blood tests.

In this study, pentostatin will be given intravenously (over 15-30 minutes) on Days 1, 2, 3, of the first week and repeated in the third week on Days 15, 16 and 17 of your treatment.

Voluntary Participation

You are free to choose to participate or decline participation now or at any time in your treatment course. If you decline to participate now or withdraw your consent after treatment is started, standard GVHD therapy will be available to you. None of your rights are waived by enrolling in this research study and therapy for any medical conditions will continue even if you withdraw from the study. Your doctors have made themselves available to answer any of your questions about participation in this study and will continue to do so throughout your treatment. Throughout the study, the researchers will tell you of new information that might affect your decision to remain in the study. If you have additional questions about the study or about your rights as a participant in this study, you may contact [the Principal Investigator at your transplant center]. If you have any questions or concerns, please ask your doctors or the study coordinators.

You can be taken off the study (with or without your consent) for any of the following reasons:

- You do not qualify to be in the study because you do not meet the study requirements. Ask your doctor if you would like more information about this.
- You need a medical treatment not allowed in this study.
- The investigator decides that continuing in the study would be harmful to you.
- The study treatments have a bad effect on you.
- You become pregnant and the study treatment could be harmful to the fetus.
- You are unable to keep appointments or take study drugs as directed.
- Other study-specific reasons; for example, if the dose of study drug you are taking has been found to be unsafe.

- The study is cancelled by the Food and Drug Administration (FDA) or the National Institutes of Health (NIH).

Benefits

Although this study cannot be guaranteed to be of benefit to you, it is hoped that your taking part may help in the treatment of your GVHD. A possible advantage of this study is that one of the study drugs may treat GVHD better than the others. However, you may not benefit from this treatment. It is also hoped that the information learned from this study will help your doctors treat patients in the future who get GVHD.

Compensation

In the event that this research activity results in an injury, treatment will be available including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to your insurance company. If you think you have suffered a research related injury, let the study physicians know right away. Unexpected side effects or accidents might result in your getting sicker than anticipated in the course of this treatment. All available medical care will be provided to you, but you and your insurance company (3^{rd} party payer) are responsible for the costs of all such care.

Confidentiality

All necessary steps will be undertaken to avoid your being identified in any public presentations. However, the results of this study treatment may be published in scientific journals in the future, but no one patient (including you) will be identified. Information concerning your transplant course may be reviewed or transmitted to national and international transplant registries, including the Center for International Blood and Marrow Transplant Research (CIBMTR), Autologous Blood and Marrow Transplant Registry (ABMTR), the National Marrow Donor Program (NMDP), to the Food and Drug and Administration (FDA), Data Coordinating Center of the National Institutes of Health (NIH), Blood and Marrow Transplant Clinical Trials Network (BMT CTN), and to other authorized study organizations. However, you will not be identified by name in publications or reports coming from such groups or review.

Information related to or resulting from your stem cell transplant will be reported to the CIBMTR. The CIBMTR is a voluntary organization of basic and clinical scientists working together in an effort to gather information on results of stem cell and marrow transplants. This information is used to guide clinical decisions and identify ways to improve transplant outcomes. Scientific data or medical information (not identifiable with you) that could be useful to others may be presented at meetings and/or published in medical journals.

You will be given a copy of this form.

HIPAA[1] authorization to use and disclose individual health information for research purposes

a. Purpose: As a research participant, I authorize the Principal Investigator and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study entitled *Initial Systemic Treatment of Acute GVHD: A Phase II Randomized Trial Evaluating Etanercept, Mycophenolate Mofetil (MMF), Denileukin Diftitox (ONTAK), and Pentostatin in Combination with Corticosteroids*

b. Individual Health Information to be Used or Disclosed: My individual health information that may be used or disclosed to conduct this research includes: demographic information (e.g., age, date of birth, sex, weight), medical history (e.g., diagnosis, complications with prior treatment), physical examination findings, and laboratory test results obtained at the time of work up and after treatment (e.g., blood tests, biopsy results).

c. Parties Who May Disclose My Individual Health Information: The researcher and the researcher's staff may obtain my individual health information from:

(*list hospitals, clinics or providers from which health care information can be requested)*

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d. Parties Who May Receive or Use My Individual Health Information: The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

- Principal Investigator and the researcher's staff
- Dr. Dan Weisdorf, Study Chairperson and staff/laboratories at University of Minnesota
- Staff/laboratories identified in the protocol for the evaluation of other laboratory samples; e.g., Dr. Pamela Jacobson/University of Minnesota and Dr. Brian Nickoloff/Loyola University of Chicago
- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH), study sponsors
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), data coordinating center
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)

[1] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

e. Right to Refuse to Sign this Authorization: I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any research-related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

f. Right to Revoke: I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

g. Potential for Re-disclosure: My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected. Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

h. This authorization does not have an expiration date.

Blood Samples for Research
You will have tests to measure the effect of GVHD and the drugs on your immune system.

For these tests you will need to give a blood sample (3-5 teaspoonsful) at Days 0, 14 and 28 of the study, and 1 teaspoonful on Day 90. If your GVHD comes back, you will also need to give 1 teaspoonful of blood.

Additionally, to understand how certain genes may affect the development of GVHD in you, some genes that affect inflammation hormones (cytokines) will be studied in your blood or in a swab of the tissues in your mouth.

Skin Samples for Research
GVHD can cause a skin rash. To study how GVHD may affect your skin and the genes in your skin cells, a small skin sample (skin biopsy) will be taken before you start treatment and another 28 days after you start treatment for your GVHD. The skin samples are taken from an area where you currently have a rash. Each sample is a 1/8" (one-eighth of an inch) circle of skin.

These skin samples are not required for your treatment, but will be used to study what happens to your skin during treatment. This may better explain how acute GVHD injures the skin cells and the effect of treatment by the different study drugs.

The samples collected for research purposes will be sent to laboratories that have contracts with the National Marrow Donor Program (NMDP) to conduct these research tests. They will be labeled with unique codes that do not contain information that could identify you. A link to this code does exist. The link is stored at the Data Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The staff at the laboratories where your samples are being tested do not have a link to this code. Your samples will be stored at these laboratories until the entire sample has been used for the research tests or until the end of the study.

If any of your samples are leftover after the research studies are completed, these samples will either be destroyed or be sent to the National Heart Lung and Blood Institute (NHLBI) sample repository in Maryland. If your leftover samples are sent to the repository, they will be given an anonymous code. These leftover samples stored at the repository can never be linked to you. Any research performed on these leftover samples must first be approved by an advisory panel at the NHLBI.

Research Samples are Optional
It is your choice to volunteer to give these extra blood and skin samples. Your blood samples and skin biopsy will be collected confidentially (your name will not be attached to them). Only the study doctors or personnel working with them will study your skin and blood samples.

If you agree to allow your blood and skin samples to be used for research, you can change your mind later. If you do, please contact [the Principal Investigator at your transplant center] in writing to state that you are withdrawing permission for your blood or your skin biopsy to be used for research. His mailing address is on the first page of this consent form. Any unused blood or biopsy tissue will be destroyed if you withdraw your permission.

If you choose not to participate in this additional research there will be no change in your care.

Please indicate your choice(s) below:

Blood Samples

_____ I give permission to use additional samples of my blood for GVHD-related research.

_____ No, I do not wish samples of my blood to be used for additional research.

Skin Samples

_____ I give permission to use additional sample of my skin for GVHD-related research.

_____ No, I do not wish samples of my skin to be used for additional research.

Patient's Signature:_____

Date:_____

Statement of Consent

I consent to participate in this study treatment plan for GVHD including the use of prednisone plus one of four study drugs that will be assigned to me in random fashion. I have asked questions that I have now and have received answers. I know that I can ask additional questions in the future.

Signature Date

I have explained in full the details of this study treatment plan for acute GVHD and answered as best as possible all questions that were asked.

Signature of Counseling Physician Date