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Protocol Title: Early Intervention with Eculizumab to Treat Thrombotic Microangiopathy/atypical Hemolytic Uremic Syndrome (TMA/aHUS)-associated Multiple Organ Dysfunction Syndrome (MODS) in Hematopoietic Stem Cell Transplant (HCT) Recipients

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CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: EARLY INTERVENTION WITH ECULIZUMAB TO TREAT THROMBOTIC MICROANGIOPATHY/ATYPICAL HEMOLYTIC UREMIC SYNDROME (TMA/AHUS)-ASSOCIATED MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS) IN HEMATOPOIETIC STEM CELL TRANSPLANT (HCT) RECIPIENTS

STUDY NUMBER: 2018-7119C

STUDY SPONSOR: Stella Davies, MBBS, PhD, MRCP

Name of Principal Investigator:
Sonata Jodele, MD

Telephone Number:
(513) 636-5917 during business hours.
After business hours please call (513) 636-4200 and ask for the BMT physician on call.

Subject Name: _____ Date of Birth: _____/_____/_____

Throughout this document, references to "You" may stand for either the research study subject or for the parents or legal guardians of the research study subject if the subject is under 18 years of age or otherwise unable to legally give informed consent to participate in the research study. The signature(s) at the end will clarify whether the research study subject is signing this consent form on their own behalf or via a legal guardian or legal personal representative.

INTRODUCTION

We are asking you to be in a research study so that we can learn new information that may help others. If you decide not to be in this study, we will still take good care of you. If you decide to be in this study, you may change your mind at any time during the study and you can stop being in the study. Take all the time you need to make your choice. Ask us any questions you have. It is also okay to ask more questions after you decide to be in the study. You can ask questions at any time.

WHY ARE WE DOING THIS RESEARCH?

The purpose of this research study is to study if early medical treatment with a drug called eculizumab will help control thrombotic microangiopathy/atypical hemolytic uremic syndrome (TMA/aHUS) (further referred to as "TMA") and prevent TMA associated organ injury (kidney, heart, lung, brain, bowel and others). TMA is the injury of small vessels in the body that result from small thrombi or blood clots in the vessels which block blood flow to the organs. TMA is one of the hematopoietic stem cell transplant (HCT) complications that occurs in about one third of patients. Some patients can have severe TMA presentation that can result in significant organ damage and death.

Over years of research, we learned that TMA is caused by an over activated complement system. The complement system is one of our important defense systems that helps the body fight infections. If this system gets over activated during the transplantation process from high dose chemotherapy or infections like viruses and bacteria, the complement itself can cause organ damage resulting in TMA. It is important to treat TMA early, since it is very difficult to reverse significant organ damage when it occurs due to TMA.

In this study, we have an opportunity to use medical therapy with a new complement blocking medication called eculizumab (Soliris). Eculizumab blocks the complement system and prevents organ damage from TMA. Eculizumab is a type of study drug called a "biologic", which means that it comes from a living source (such as humans or animals). It has been approved for use in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH), a rare disease that destroys red blood cells, and in patients with Atypical Hemolytic Uremic Syndrome (aHUS), which is a rare genetic disorder that causes life-threatening blood clots in the body. However, eculizumab has not been looked at in clinical studies in patients receiving HCT. Our transplant group has clinical experience using this medication in HCT patients with high risk TMA. To date we have treated more than 50 children and young adults with severe TMA and we were able to significantly improve survival and organ damage in most of these patients. Despite our experience, we need to study this medication and its effectiveness in TMA after HCT in well-structured clinical studies.

You are being asked to participate in this research study because you have TMA that has a high risk of significant organ (kidney, lung, heart, bowel, brain) injury and even death. Our clinical experience indicates that eculizumab could be beneficial to treat your condition if this medication is used as an early treatment.

We anticipate approximately 21 patients will participate in this research study in four different transplant centers, Cincinnati Children's Hospital (CCHMC), Children's Hospital Los Angeles (CHLA), Children's Hospital of Philadelphia (CHOP), and Dana-Farber Cancer Institute (DFCI)/Boston Children's Hospital (BCH).

WHO IS IN CHARGE OF THE RESEARCH?

Dr. Sonata Jodele is the researcher at Cincinnati Children's Hospital Medical Center (CCHMC) who is in charge of this study. Dr. Jodele has a pending patent application for the use of eculizumab to treat TMA.

Alexion Pharmaceuticals will provide eculizumab for this research study.

WHAT WILL HAPPEN IN THE STUDY?

If you agree to participate in this study you will be started on the complement blocking agent eculizumab (Soliris). Eculizumab will be given as an intravenous infusion (IV) over 60 minutes into a peripheral IV or central line. You will receive 18 doses of this medication over 24 weeks. The dose given to you will be based on your weight. The study doctors will closely look at your organ function, including laboratory studies that will include frequent checks of blood counts, kidney/liver function, urinalyses, or other tests as clinically needed. Study doctors will also look at the complement system

markers and eculizumab levels in the blood to follow TMA response. Some of these laboratory study results will be used for research purposes to determine the best eculizumab dosing schedule for future transplant patients. In addition, research samples will be collected and sent to Alexion for drug level and biomarker testing.

You may receive eculizumab for fewer than 24 weeks if the study doctor thinks it is in your best interest. The number of weeks may be shortened if the TMA is adequately controlled or resolved and additional doses would not be of benefit or if continuation of eculizumab would interfere with other clinical interventions. The study doctor may decide to restart eculizumab if your clinical condition changes. Whether or not eculizumab is stopped early, you will remain in the study through one year after your transplant.

Eculizumab can weaken your immune system to fight particular bacteria, like N. Meningitides, which may cause bacterial meningitis. Anti-meningococcal vaccine is usually required for patients receiving eculizumab treatment. However, due to your immunocompromised status, your treating doctor will determine if the vaccine can be administered to you. Whether you receive the vaccine or not, you will be required to take antibiotics to prevent infection for the duration of eculizumab treatment and for several weeks after treatment is completed (until certain TMA labs return to normal levels). Additionally, you will be receiving routine transplant care and monitoring prescribed by your treating doctor.

Participation in the study will not affect how your primary disease is being treated during transplant and it does not affect your participation in other clinical studies. After eculizumab treatment is completed you will be closely followed by the bone marrow transplant team for one year, using the same monitoring tests and clinic visits as required for routine post-transplant care.

If you receive a special treatment called fresh frozen plasma (FFP) or therapeutic plasma exchange (TPE) for any reason during study treatment, an extra dose of eculizumab will be administered within about 60 minutes after each special treatment. Fresh frozen plasma (FFP) or therapeutic plasma exchange (TPE) will reduce effectiveness of eculizumab and for that reason, an additional dose of this drug is needed.

During this study, we would like to learn new information about eculizumab and how well it works for TMA. We would like to store leftover blood and urine samples that are taken for clinical tests, so they can be used to look at disease and organ function biomarkers (biomarkers are important biological ‘indicators’ which can be measured from blood and urine samples), complement activity tests, and eculizumab drug levels in the blood.

In addition, all transplant patients are invited to submit samples to the CCHMC HSCT Repository. If you are participating in the repository, some samples required for this study may be obtained from the repository. If you are not participating in the repository already, we will request to obtain samples as described below. These samples will be used for research to better understand TMA, complement system, and the effects on the body.

Blood, urine, and stool samples will be collected weekly while receiving study medication. Once you are no longer receiving study medication, weekly blood, urine, and stool samples will be collected as

long as the study medication remains in your blood. These samples will also be collected at 6 months and 1 year post-transplant during your routine clinic visits.

Peripheral blood will be obtained when undergoing clinically indicated blood draws whenever possible. We will not draw more blood than what we consider to be a safe amount to draw at one time for transplant patients. This may be split and drawn over 2 days depending on weight. Less blood will be collected if there are concerns from your study doctor about the amount of blood to be drawn.
Other tissue samples, like bone marrow, tissue cells or fluid will only be collected and stored in the tissue repository if these samples are already being obtained as part of your standard clinical care as prescribed by your doctor for the treatment of your primary or other transplant complication. Genetic material obtained from the blood, tissue cells or saliva may be used to study genes that can be associated with TMA or other transplant complications. If a pre-transplant DNA sample is available, we may request it for a TMA-associated genetic panel.

WHAT ARE THE GOOD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

Based on our experience treating other transplant patients with TMA, we believe this therapy may be of benefit for you to control TMA and to prevent organ injury. The information learned from this research study may benefit other patients in the future.

WHAT ARE THE BAD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

Like all medicines, eculizumab can cause side effects, although not everybody will experience them. The side effects of eculizumab are usually mild or moderate. Your study doctor will discuss the possible side effects with you and explain the risks of eculizumab prior to treatment.

If you are not sure what the side effects described below are, ask your study doctor to explain them to you.

Eculizumab blocks complement and can weaken your body's ability to fight certain infections, in particular N. Meningitides that can cause bacterial meningitis. After the transplant process you are immune compromised, have much higher risk of infections than a person not receiving transplant and will be receiving medication to prevent infections as part of your clinical care. In addition, we will take extra steps to ensure your safety during eculizumab treatment and will require you to take antibiotics. You may receive an anti-meningococcal vaccine as determined by your treating doctor.

Eculizumab side effects

Very Common (occurring in at least 1 in 10 patients)
Headache

Common (occurring in 1 or more out of 100 patients and less than 10 in 100 patients)
• Decreased blood clotting cells, decreased white blood cells, increased breakdown of the blood cells • Diarrhea, vomiting, nausea, abdominal pain, constipation, stomach discomfort after meals • Swelling, chest discomfort, fever, chills, feeling tired, weakness, flu-like illness • Severe allergic reaction • Severe infection in the blood stream or body tissues caused by meningococcus, infection in the joints, upper respiratory tract infection, common cold, bronchitis, cold sores, infection of the urinary system,

viral infection, fungal infection caused by a fungus called aspergillus • Decreased appetite • Joint pain, muscle aches, muscle spasms, bone pain, back pain, neck pain, pain in the arms and legs • Dizziness, altered or impaired sense of taste • Difficulty breathing, cough, stuffy nose, throat irritation or pain, runny nose • Rash, hair loss, itchy skin • Low blood pressure

Uncommon (occurring in 1 or more out of 1000 patients and less than 1 in 100 patients)
• Infusion site pain, infusion related reaction, hives • Severe infection, pneumonia, stomach flu, cystitis, abscess, cellulitis, fungal infection, flu • Abnormal liver function tests

If you would like more information about other uncommon side effects, please talk with your doctor.

In addition, serious meningococcal infections have been reported in patients receiving Eculizumab. Meningococcal infections can rapidly become life-threatening or fatal.

POTENTIAL LIFE-THREATENING RISKS
Patients who receive Eculizumab will have their immune system impaired, meaning that your ability to fight off viral and bacterial infections may be affected.

Patients treated with Eculizumab are at increased risk for development of serious meningococcal infections. Meningococcal infections can rapidly become life-threatening or fatal especially if not recognized and treated early. You will be required to take antibiotics to prevent infection for the duration of eculizumab treatment and for several weeks after treatment is completed (until certain TMA labs return to normal levels). You may also receive a vaccination against meningococcal infections. Vaccination alone may not be sufficient to prevent infection with *Neisseria meningitidis*.

You will be given a detailed Patient Safety Information Card to carry at all times. This safety card explains that you are taking part in a research study and contains important safety information about the potential risk of meningococcal infection, a description of the study drug, and emergency contact information. Show this card to any doctor involved in your treatment/medical care.

Eculizumab treatment may reduce your natural resistance to infections, especially meningococcal infection which requires immediate medical attention. If you experience any of the following symptoms, you should immediately call your study doctor:

- Headache with nausea or vomiting
- Headache with fever
- Headache with a stiff neck or back
- Fever of 103°F (39C) or higher
- Fever and a rash
- Confusion
- Severe muscle aches with flu-like symptoms
- Sensitivity to light

If you cannot reach your study doctor, go to an emergency department immediately and show them

the card.

Even if you discontinue study participation, keep this Patient Safety Information Card with you for 3 months after the last treatment with eculizumab, since side effects may occur a long time after the last dose of eculizumab.

If you experience any of these symptoms, you need to be seen by a physician as quickly as possible. Early physician evaluation is important.

The vaccination against Neisseria meningitidis that you may receive can cause temporary local inflammation at the injection site.

A blood draw may involve minor pain, bleeding, bruising, and a risk of infection. There is a small risk that your protected health information may be released to an unauthorized person.

There may be other risks that we do not know about yet.

WHAT ARE THE REPRODUCTION RISKS?

If you are a female of childbearing age there may be risks that you should know about. If you become pregnant, eculizumab may involve risks to your embryo, fetus or unborn child that are currently unknown. You must use a method of birth control from the time you sign consent for the study until 5 months following your last dose of study drug. Your study doctor can discuss appropriate methods of birth control with you. If you should become pregnant during the study, you must notify your study doctor immediately.

WITHDRAWAL OF YOUR CONSENT TO PARTICIPATE IN THIS STUDY

You may decide that you no longer want to participate in this research study. This is considered as withdrawal of your consent from participation in this study. You have the right to cancel this consent at any time by giving written notice to Dr. Jodele. The study doctors will continue to retain and use any research results that have already been collected for the study evaluation. No further study-related activities will take place.

REASONS WHY YOU MIGHT BE WITHDRAWN FROM THE STUDY

In addition, your participation may also be terminated by the study doctor or the sponsor without regard to your consent if you need additional medication, violate the study plan, experience a study-related injury or if the study doctor and/or sponsor feel it is in your best interest, or for administrative reasons.

If you decide to discontinue or your participation is terminated, you will be required to go through the termination procedures and complete the follow-up visit for your own safety. You should keep in contact with your study doctor to let him/her know your progress and to ensure you have not had any adverse effects from the study drug.

WHAT OTHER CHOICES ARE THERE?

Instead of being in this study, you can choose not to be in it. You may also decide to receive supportive care only. You can receive the drug, eculizumab, without participating in this study.

Participation in this research study is completely voluntary. Your care will not be altered or compromised if you do not participate.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE?

Making sure that information about you remains private is important to us. To protect your privacy in this research study, we will store study data on password protected computers and documents will be stored under lock and key with restricted access to only qualified personnel involved in this research study. You will not be identified in any publication resulting from any research using this data or these samples.

Study data/results will be shared with Alexion Pharmaceuticals. The data/results sent to Alexion will not include any identifiable information about you.

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.

The Food and Drug Administration (FDA) may choose to inspect your records since you are a subject in this investigation of a drug not approved for your disease.

To help protect your confidentiality, a Certificate of Confidentiality (CoC) is issued from the National Institutes of Health (NIH). This certificate may prevent the researchers from being forced (for example, by court subpoena) to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding. However, a CoC does not prohibit the researcher from disclosing information about you or your involvement in this research that you have agreed to disclose or make available. For example, if you or your legally authorized representative request in writing that information about you or your participation in the research be released to your insurance company, the researcher may not use the CoC to withhold this information. This means that you and your family should actively protect your privacy. Finally, the researcher is not prevented from taking steps, including reporting to appropriate authorities, to prevent child abuse or serious harm to yourself or others.

WHAT IF WE LEARN NEW INFORMATION DURING THE RESEARCH?

The study doctor will tell you if they find out about new information from this or other studies that may affect your health, safety or willingness to stay in this study.

WILL IT COST YOU ANYTHING EXTRA TO BE IN THE RESEARCH STUDY?

You or your insurance company will be billed for all standard clinical care, including the cost of the

required antibiotic or vaccine administered with this study drug. The cost of the study drug and any research laboratory tests will be provided by the study (including samples to be sent to Alexion).

WILL YOU BE PAID TO BE IN THIS RESEARCH STUDY?

You will not be paid for participating in this research study.

WHAT HAPPENS IF YOU ARE INJURED FROM BEING IN THIS STUDY?

If you believe that you have been injured as a result of this research you should contact Dr. Jodele at (513) 636-5917 as soon as possible to discuss the concerns. Treatment for injuries is available at CCHMC. If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in a research study. If possible, you should give them a copy of this consent form.

CCHMC follows a policy of making all decisions about compensation for the medical treatment of physical injuries that happened during or were caused by research on an individual basis.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions, concerns, or complaints about this research study you can contact the study person listed on page 1 of this document.

If you would like to talk to someone that is not part of the research staff or if you have general questions about your research study rights or questions, concerns, or complaints about the research, you can call the CCHMC Institutional Review Board at 513-636-8039.

WHAT ELSE SHOULD YOU KNOW ABOUT THE RESEARCH?

Your samples and medical information will be stored indefinitely, including after your treatment at CCHMC is over. This consent, unless you choose to withdraw it, shall remain in effect for as long as the samples and medical information are retained. If you choose to withdraw from the study, no further study-related activities will take place and stored samples will be destroyed. Medical information collected prior to your withdrawal of consent will be retained. Samples and medical information that have already been distributed to researchers prior to your withdrawal of consent as well as any data obtained from the distributed sample(s) will not be destroyed.

The samples may be used by researchers at Cincinnati Children's Hospital Medical Center or at other institutions if some are left over after the tests for this study. The researchers must get local Institutional Review Board (a group that is in charge of regulating research done on people) approval prior to requesting data and/or samples left over from this study, if applicable.

If your samples and/or data are released to institutions other than Cincinnati Children's Hospital Medical Center, we will remove any information that can identify you.

AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

To be in this research study you must also give your permission (or authorization) to use and disclose (or share) your "protected health information" (called PHI for short).

What protected health information will be used and shared during this study?
CCHMC will need to use and share your PHI as part of this study. This PHI will come from:
- Your CCHMC medical records
- Your research records

The types of information that will be used and shared from these records include:
- Laboratory test results, diagnosis, and medications
- Reports and notes from clinical and research observations
- Imaging (like CT scans, MRI scans, x-rays, etc.) studies and reports
- If applicable, information concerning HIV testing or the treatment of AIDS or AIDS-related conditions, drug or alcohol abuse, drug-related conditions, alcoholism, and/or psychiatric/psychological conditions (but not psychotherapy notes).

Who will share, receive and/or use your protected health information in this study?
- Staff at all the research study sites (including CCHMC)
- Personnel who provide services to you as part of this study
- Other individuals and organizations that need to use your PHI in connection with the research, including people at the sponsor and organizations that the sponsor may use to oversee or conduct the study.
- The members of the CCHMC Institutional Review Board and staff of the Office of Research Compliance and Regulatory Affairs.

How will you know that your PHI is not misused?
People that receive your PHI as part of the research are generally limited in how they can use your PHI. In addition, most people who receive your PHI are also required by federal privacy laws to protect your PHI. However, some people that may receive your PHI may not be required to protect it and may share the information with others without your permission, if permitted by the laws that apply to them.

Can you change your mind?
You may choose to withdraw your permission at any time. A withdrawal of your permission to use and share your PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share PHI you need to notify the study doctor, listed on the first page of this document, in writing. Your request will be effective immediately and no new PHI about you will be used or shared. The only exceptions are (1) any use or sharing of PHI that has already occurred or was in process prior to you withdrawing your permission and (2) any use or sharing that is needed to maintain the integrity of the research.

Will this permission expire?
Your permission will expire at the end of the study. If the study involves the creation or maintenance of a research database repository, this authorization will not expire.

Will your other medical care be impacted?

By signing this document you agree to participate in this research study and give permission to CCHMC to use and share your PHI for the purpose of this research study. If you refuse to sign this document you will not be able to participate in the study. However, your rights concerning treatment not related to this study, payment for services, enrollment in a health plan or eligibility of benefits will not be affected.

FUTURE USE OF DATA AND SPECIMENS

The study investigators would like to use your study data and any leftover samples for future research. The data and samples will be given a unique code and will not include information that can identify you. If you agree that your data and samples may be used for future research, you may change your mind at any time. Please initial and date below to specify your consent or refusal to the use of your study data and samples for future research.

I agree to the use of my study data and leftover samples for future research.

☐ **Yes** Initials _____ Date _____

☐ **No** Initials _____ Date _____

SIGNATURES

The research team has discussed this study with you and answered all of your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether you should participate in this research you will document your consent by signature below.

You will receive a copy of this signed document for your records.

_____ _____
Signature of Research Participant Indicating Consent — Date

_____ _____
Signature of Parent or Legally Authorized Representative* — Date

_____
* If signed by a legally authorized representative, a description of such representative's authority must be provided

_____ _____
Signature of Individual Obtaining Consent — Date

The signature line below is to be used only when an interpreter or a witness is required for the consent process for non-English speaking participants/families.

Check this box if not applicable: ☐

_____ _____
Signature of Person Present During Consent — Date