CONSENT FORM TO BE PART OF A RESEARCH STUDY

Title of Research: **Early Treatment of Cytokine Storm Syndrome in COVID-19**

UAB IRB Protocol #: **IRB-300005684**

Principal Investigator: **W Winn Chatham MD**

Sponsor: **UAB Department of Medicine**

Supported By: **Swedish Orphan Biovitrum (SOBI)**

General Information	You are being asked to take part in a research study. This research study is voluntary, meaning you do not have to take part in it. The procedures, risks, and benefits are fully described further in the consent form.
Purpose	The purpose of this study is to determine whether treatment with the drug anakinra improves the outcomes of patients with COVID-19 virus infection who have features of Cytokine Storm Syndrome (CSS). CSS is a complication that can occur in some viral infections that can be associated with development of severe lung and other organ inflammation. For patients found to have features of CSS, the study will determine good and bad effects of using the experimental drug anakinra compared to standard treatment and supportive care for treatment of COVID-19 virus infection.
Duration & Visits	You will be in the treatment phase of this study for ten days. After the ten day treatment period your progress will be recorded through the time of your hospital discharge. You will be asked to return for a blood draw for antibody testing 30 days after the study treatment started. You will be contacted by phone 60 days after the study treatment to document whether you have had any infections or need for supplemental oxygen.
Overview of Procedures	If you have findings of Cytokine Storm Syndrome and agree to proceed with the experimental treatment in this study, a computer will assign you by chance (randomization) to one of the study treatments. You will either get the study drug anakinra or the saline placebo injected beneath your skin every 6 hours for a total of 10 days. After you begin to receive the study drug, you will have blood drawn daily and your doctor and study team will watch you for side effects and monitor your progress.
Risks	The most common side effects associated with anakinra treatment are: • Local site reaction to the injections • Headaches • Fever • Nausea • Joint pains • Nasal congestion/sore throat A very uncommon side effect of anakinra treatment can be can be severe allergic hypersensitivity reactions with anaphylaxis
Benefits	You may or may not benefit from participation in this study. Treatment with anakinra may help prevent COVID-19 severe lung and organ complications.

Alternatives	If you do not want to take part in the study you can continue to receive the customary supportive care for patients with COVID-19 infection.

Purpose of the Research Study

We are asking you to take part in a research study because you have been admitted to the hospital with COVID-19 virus infection and have blood test results that indicate you may be developing a severe complication of the infection called Cytokine Storm Syndrome (CSS).

The purpose of this research study is to determine whether treatment with the biologic drug anakinra stops the progression of CSS and the development of lung and other organ complications that can be associated with CSS. If not adequately treated, CSS can result in death in a significant number (up to 50% or half) of affected patients. This study will also determine whether patients admitted with COVID-19 virus infection who develop CSS carry genetic risk factors known to be associated with the development of CSS.

Interleukin-1 (IL-1) is a product of the immune system that causes fever as well as the production of many other immune system products that can contribute to organ damage in patients with CSS. Anakinra is an IL-1 blocking drug approved by the U.S. Food and Drug Administration (FDA) to treat rheumatoid arthritis as well as other diseases associated with abnormal immune system production of IL-1. Anakinra has also been studied in the treatment of patients with sepsis, a severe complication of bacterial infections. In these studies, treatment with anakinra did not increase overall survival from sepsis but also did not result in worse outcomes in the people who were treated with anakinra. However, among patients in these studies who had laboratory features seen in CSS, survival was increased in those patients given anakinra compared to those given placebo treatment.

Anakinra is not approved by the FDA to treat CSS in COVID-19, so the use of anakinra in this study is considered experimental. This study is a pilot study, which means it is a research study to determine whether a treatment has possible effectiveness compared to standard treatment and is safe to administer to patients with the disease it is being used to treat.

We will enroll 30 participants at UAB into this study.

Study Participation & Procedures

If you agree to join the study, you will have research-related blood tests performed in addition to the blood tests drawn to monitor your condition as part of the standard supportive care for treatment of COVID-19 infection. The blood samples obtained for research purposes will be drawn daily at the time blood is drawn for tests needed for your routine care.

Day 1: After signing the consent form, you will:
Have blood drawn (2 tbsp. or 30 ml) for research related lab studies to confirm. if there are signs of CSS, and whether you meet the criteria for starting the experimental treatment protocol with anakinra.
If you meet the inclusion criteria for and agree to proceed with the study randomization will occur. Randomization means you will be randomly picked (like the flip of a coin and 50/50 chance for either group) by a computer to be in one of the two groups:

1. Experimental Group - treatment with anakinra injections

OR

2. Control Group - receive placebo injections with a placebo salt solution (normal saline)

During the treatment protocol this will be a double-blinded study —Dr. Chatham, Dr. Cron, your treating physicians and nurses, and also you will not know the treatment group to which you have been assigned.

In addition to the standard of care treatment for COVID-19 virus infection, these tests and treatments will be performed if you participate in this study:

Day 0 (first day of treatment protocol):

- Recording of your vital signs, needed ventilation and oxygen support, heart function, kidney function.
- Research related blood tests to assess severity of CSS (3 tbsp. or 45 ml blood)
- Blood sample for genetic testing to see if you have genetic traits associated with risk of CSS
- Injection beneath your skin of the research study drug anakinra (100 mg in 0.7 ml) or placebo saline injection every 6 hours

Days 1-9 (following initiation of treatment protocol)

- Recording your vital signs, needed ventilation and oxygen support, heart function, kidney function.
- Research related blood tests to monitor presence and severity of CSS (2 tbsp. or 30 ml blood)
- Injection beneath your skin of research study drug anakinra (100 mg in 0.7 ml) or placebo saline injection (0.7 ml) every 6 hours

Day 10 (following initiation of treatment protocol:

- Recording of your vital signs, needed ventilation and oxygen support, heart function, kidney function.
- Research related blood tests to assess presence and severity of CSS (3 tbsp. or 45 ml blood)

If on or after Day 5 but before Day 10 your condition has improved such that you no longer require supplemental oxygen and your blood test results indicating CSS have returned to normal or improved more than 75% compared to when you entered the study, the dosing of the anakinra or placebo will be decreased to once every 12 hours until the study treatments end on Day 10.

After Day 10 your vital signs, needed ventilation and oxygen support, heart function, kidney function will continue to be tracked and recorded until you are discharged from the hospital.

Day 30: You will be asked to return for a blood draw to determine if you have developed antibody to the virus as well as record your need (if any) for supplemental oxygen or any infection complications since discharge from the hospital.

Day 60: You will be contacted by phone 60 days after the study treatment to document whether you have had any infections and any needs for supplemental oxygen.

Unexpected adverse events or need for intubation will be recorded through the time of hospital discharge.

The study doctor will discuss with you your responsibilities as a participant.

Additional Information:
Your de-identified private information (private information with all identifiers removed) may be used for future research studies or distributed to another researcher for future research studies without additional informed consent.

The clinical results (including individual research results) obtained during this study will not be returned to you.

This research involves genetic testing, including whole genome sequencing, which is the process of mapping all of an individual's genes. You will be informed of the results of any genetic studies performed to determine whether you carry genetic traits known to be associated with increased risk of CSS.

Risks and Discomforts

Blood Drawing Risks: Possible side effects from drawing blood include dizziness, redness and swelling of the vein, pain, bruising, or bleeding from the site of the needle puncture. There is also a chance of infection. Given your condition and the amount of blood being drawn during the course of the study, there is also a risk of developing anemia (low blood count).

You may have some side effects from taking the study drug anakinra.

- Injections of anakinra or injections of the placebo saline may be associated with mild pain, redness and swelling that appear at the injection sites.
- Risks or occurrences that were reported in studies with anakinra in adults with Rheumatoid Arthritis (RA) and in children with Neonatal Onset Multisystem Inflammatory Disease (NOMID) and how often these occur are show in the table below. Some of the reported occurrences may occur due to the underlying disease being treated. There is no reason to believe that risks will be different for people with Covid-19 associated CSS, but CSS alone can cause many of the listed central nervous system, gastro-intestinal, liver, and blood cell count occurrences. There may be other risks that are unknown to us at this time.

Most common, greater than 10%:	**Other common, 1% - 9%**	**Serious, rare, less than 1%**
Central nervous system: Headache (12% to 14%), Fever (12%) Gastrointestinal: Nausea (8%) Local Injection site reaction: Skin rash, redness, swelling at injection site (RA:≤71%; mild: 73%; moderate; 24%; severe: 3%; NOMID: 16%) Neuromuscular & skeletal: Joint pains (6% to 12%) Respiratory: Sinus, throat irritation (12%) Miscellaneous: Infection (39% versus 37% in placebo; serious infection 2%- 3%)	Gastrointestinal: Diarrhea (7%) Hematologic: Low white blood cells (neutropenia)(5% to 8%)	Liver inflammation Allergic reactions with lip swelling, limb swelling, itching, skin rash, fast heartbeat, hives Low platelets in blood Infections: Skin (cellulitis) Lung (pneumonia) Lung scarring Malignancies: Cancers of lymph organs (lymphoma) Melanomas

Risk of randomization: You will be assigned to a group by chance, which may prove to be less effective or to have more side effects than the other study group or alternatives.

There may also be risks that are unknown at this time. You will be given more information if other risks are found.

Risks to women who may be pregnant: Anakinra has not been formally studied in pregnant women, but anakinra has been used in pregnant women with no reported adverse outcomes to the developing fetus.

Benefits

You may not benefit directly from taking part in this study. However, this study may help us better understand how to treat Covid-19 viral infections in the future.

You will be assigned to a group by chance, if you are assigned to the anakinra experimental treatment group, you may have more or less benefits than the placebo group.

Alternatives

Remdesivir is an anti-viral drug that has been show to decrease the average length of hospitalization and time to recovery in populations of patients hospitalized with Covid-19. It is not known whether remdesivir is of benefit in treating CSS associated with Covid-19. Your doctors may offer to treat you with remdesivir if it is available to treat you. If remdesivir is available, your participation in this study will not affect the decision whether to treat you with remdesivir. If you are treated with remdesivir, you may still participate in this study There are currently no other proven beneficial treatments for Covid-19 infection. You do not have to participate in this study and can continue to receive supportive care for the Covid-19 infection and complications. The study doctor will discuss with you the alternatives to participation and their risks and benefits.

Confidentiality and Authorization to Use and Disclose Information for Research Purposes

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you.

What protected health information may be used and/or given to others?
All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of any kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills; any other information related to or collected for use in the research study, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes; records about any study drug you received or about study devices used; and consent forms from past studies that might be in your medical record.

Your consent form will be placed in your medical record at UAB Health System. This may include either a paper medical record or electronic medical record (EMR). An EMR is an electronic version of a paper medical record

of your care within this health system. Your EMR may indicate that you are on a clinical trial and provide the name and contact information for the principal investigator.

If you are receiving care or have received care within this health system (outpatient or inpatient), results of research tests or procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing medical record.

All information within your medical record can be viewed by individuals authorized to access the record.

All medical information related to your participation in the study within your medical record can be viewed by individuals authorized to access the record.

A description of this clinical trial is available on www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Who may use and give out this information?
Information about your health may be used and given to others by the study doctor and staff. They might see the research information during and after the study.

Who might get this information?
All individuals/entities listed in the informed consent document(s), including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere). Your information may also be given to the sponsor of this research. “Sponsor” includes any persons or companies that are working for or with the sponsor, or are owned by the sponsor, or are providing support to the sponsor (e.g., contract research organization).

Information about you and your health which might identify you may be given to:

- the Office for Human Research Protections (OHRP)
- the U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- the University of Alabama at Birmingham - the physicians, nurses and staff working on the research study (whether at UAB or elsewhere); other operating units of UAB, UAB Hospital, UAB Highlands Hospital, University of Alabama Health Services Foundation, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the UAB IRB and its staff
- the billing offices of UAB and UAB Health Systems affiliates and its billing agents

Why will this information be used and/or given to others?
Information about you and your health that might identify you may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and some employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by all employers.

What if I decide not to give permission to use and give out my health information?
By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research.

May I review or copy the information obtained from me or created about me?
You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your information until after the research is completed.

May I withdraw or revoke (cancel) my permission?
Yes, but this permission will not stop automatically. The use of your personal health information will continue until you cancel your permission.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is my health information protected after it has been given to others?
If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others, including others outside of UAB, without your permission.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in it. If you decide not to be in the study, you will not lose any benefits you are otherwise owed.

You are free to withdraw from this study at any time. Your choice to leave the study will not affect your relationship with this institution or the care you receive. Contact the study doctor if you want to withdraw from the study.

You may be removed from the study without your consent if the study doctor decides it is not in the best interest of your health.

Cost of Participation

There will be no cost to you for taking part in this study. All study drugs and study-related medical care study will be provided to you at no cost during the 4 to 11 day study period.

The costs of your standard medical care will be billed to you and/or your insurance company in the usual manner.

If you are in Medicare Advantage (Medicare managed care plan), you should contact someone at your plan before you start a clinical trial. They can provide more information about additional costs you could incur from participating in clinical trials.

Payment for Participation

You will not be paid for your participation in this research.

Payment for Research-Related Injuries

UAB and SOBI have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

New Findings

You will be told by the study doctor or the study staff if new information becomes available that might affect your choice to stay in the study.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact the study doctor. You may contact Dr. Winn Chatham at 205-996-5602 or after hours by paging him at 205-934-3411

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday.

Legal Rights

You are not waiving any of your legal rights by signing this consent form.

Signatures

Your signature below indicates that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this signed consent form.

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Signature of Participant or Legally Authorized Representative Date

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Signature of Person Obtaining Consent Date

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Signature of Witness Date

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Signature of Principal Investigator Reviewing Consent Document Date