Title: Treatment of Acute Pericarditis With Anakinra

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RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

TITLE: Treatment of Acute Pericarditis with Anakinra

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Please ask the study doctor or staff to explain any information in this consent document that is not clear to you. You may review this consent form with family or friends before making your decision. In this consent form, "you" always refers to the research participant.

PURPOSE OF THE STUDY

The purpose of this study is to determine if anakinra (Kineret) can lower the inflammation and the pain that are caused by acute pericarditis. This study will enroll 14 patients.

DESCRIPTION OF THE STUDY

Acute pericarditis is a condition in which the sac around the heart (pericardium) becomes irritated and causes chest pain. An injury to the cells in pericardium, usually an infection by a virus, leads to inflammation, a process by which white blood cells come from the blood to the pericardium to repair the injury.

In acute pericarditis, the inflammation is out of control, and lasts longer than it should, causing sharp chest pain. As such, anti-inflammatory drugs are given to reduce the intensity of inflammation and alleviate the pain. Although there are no anti-inflammatory drugs specifically developed or indicated for the treatment of acute pericarditis, non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen or diclofenac, are commonly used and are effective in reducing inflammation and pain.

NSAIDs may be associated with side effects such as irritation of the stomach (gastritis), injury to the kidneys (renal failure) and increased bleeding tendency (alteration of platelet function). Moreover, NSAID treatment does not reduce the chances of having acute pericarditis again and many patients will have repeat episodes of acute pericarditis.

Colchicine is another anti-inflammatory drug that works in a different way than NSAIDs. Colchicine can be used with NSAIDS to help reduce the chances of repeat episodes of acute pericarditis. The side effects of colchicine include stomach pain, severe diarrhea and, rarely, with severely low numbers of blood cells (bone marrow suppression). There is therefore a need to find new treatments for acute pericarditis that are effective, safe, and well tolerated.

This study is designed to determine if Anakinra (Kineret™) can be an effective, safe, and well tolerated treatment for acute pericarditis. We will measure levels of inflammation and pain in patients with acute pericarditis who are having a first or recurrent episode.

Anakinra (Kineret) is a "copy" of an anti-inflammatory protein that the human body naturally produces. Since 2001, anakinra has been approved by the United States of America Food & Drug Administration (FDA) for the treatment of several inflammatory conditions, such as rheumatoid arthritis.

Anakinra has been shown to be effective in patients with severe forms of pericarditis that had not responded or had recurred despite treatment with NSAIDs or colchicine. Anakinra does not

cause toxicity to the stomach, kidney or platelets like NSAIDs, nor causes abdominal pain or diarrhea like colchicine. Anakinra may therefore be a safe and effective treatment for acute pericarditis. Anakinra has not been approved by the FDA for the treatment of acute pericarditis, and as such its use is considered investigational.

PROCEDURES

If you decide to be in this study, you will be asked to sign this **consent form** after you have had all your questions answered. The study procedures will begin within 6 hours of your arrival to the hospital. Your participation will end with an outpatient visit approximately 30 days later.

After signing this consent form, you will be asked to complete a **questionnaire** as an assessment of your pain. This one-page form will ask you questions about your pain. You will then have a **blood draw, electrocardiogram (EKG) and heart ultrasound (echocardiogram).**

The blood draw will occur with a needlestick into one of your blood vessels. If a catheter (i.e. tube) is already available for blood draws, which is common when you are admitted to the hospital, then a needlestick will not be necessary and the blood will be drawn using the catheter. The total amount of blood drawn will be approximately 1 tablespoon. Performing one or more blood draws is usually standard of care when you are in the hospital.

You will also have an **electrocardiogram (EKG)**. Electrodes will be placed on your skin and the electricity coming from your heart will be recorded. You will not feel any sensation during this test. Performing one or more EKG recordings is usually standard of care when you are being treated for acute pericarditis.

You will also undergo an **ultrasound of your heart**. During this test (known as an echocardiogram), a sensor and a small amount of gel are placed on your chest to create pictures of your heart and pericardium. Performing one or more echocardiograms is usually standard of care when you are being treated for acute pericarditis.

After you have completed each of these baseline procedures, you will receive **treatment** with 3 doses of anakinra over the next 3 days. The first dose will be given as soon as possible and you will have a repeat blood draw, EKG, and pain assessment approximately 6 hours later. The next 2 doses of anakinra will be given every 24 hours. All patients who participate in this research will receive at least 3 doses of anakinra.

Each dose of anakinra will be administered with a needle into the fat tissue underneath your skin (subcutaneous tissue). If you are in the hospital, then the hospital staff will help you with the injection. If you are at home, you or someone else will be taught to give the treatment. The dose of anakinra will be 100 mg. This is the usual dose of anakinra when it is used for other inflammatory conditions.

All patients who participate in this research will receive at least 3 doses of anakinra. After the first 3 doses of anakinra, you will be assigned to continue anakinra or to switch to “placebo” treatment, which contains only the watery solution but no active medicine. This assignment will occur randomly, like the flip of a coin. Neither you nor the study team will know whether the last 4 doses are anakinra or placebo. This is done to determine whether 3 days or 7 days of treatment is better.

During this study, anakinra will serve as the main medicine to treat your pain. You will be asked

to **grade the severity of the pain** and we will measure how the anakinra is effective and whether additional pain medications are needed.

During the first 24 hours of anakinra treatment, participation in the study may affect the timing and type of other pain medications:

- During the first 6 hours of treatment:
  - We will ask you to request additional pain medications ***only*** if the pain worsens and becomes ***unbearable*** (thus allowing to determine the effects of anakinra).
  - Treatment with NSAIDs will be ***discouraged***, favoring other analgesic treatments for pain (such as acetaminophen, codeine, tramadol, morphine, etc.) as determined by your treating physician.
- Between 6 and 24 hours of treatment:
  - **Additional pain medications can be administered for any degree of pain** (as preferred by the patient).
  - **Treatment with NSAIDs will remain discouraged**, favoring other analgesic treatments for pain, which will be determined by your treating physician.
  - The amount of pain medication will be recorded.
- After 24 hours:
  - **There will be no restrictions on the timing or the type of pain medications,** but the amount of pain medication will be monitored.

You will have 3 follow-up doctor visits after the first dose of anakinra. These will occur after 1 day, after 7 days and after 30 days. These visits will occur in the VCU Medical Center. While at home, you will be asked to record each dose of pain medication that you use while you are participating in the study. At each follow-up visit, you will have a blood draw, EKG, echocardiogram, and pain assessment. At each visit, you should bring all of your remaining study drug supply to the research clinic.

RISKS AND DISCOMFORTS

Possible side effects of Anakinra (Kineret™) may include:

- Injection site reactions, such as irritation, redness or swelling at the site of administration (approximately 1 in every 10 patients); these usually go away on their own (self-limiting)
- Headache, diarrhea, and nausea may occur (less than 1 in every 10 patients), usually mild, and self-limiting
- Neutropenia (low numbers of "neutrophils" which are a type of white blood cell) (very rare, less than 1 in every 100 patients)
- Anakinra may block your body's ability to have a fever. This means that you may not have a fever if you become sick or ill. If you are feeling sick during the study, please contact your study doctor immediately. A small increase in serious infection with Anakinra has been seen (less than 1 in every 20 patients) in patients with rheumatoid arthritis on anakinra treatment for multiple years in addition to other immunosuppressive disease-modifying agents, like methotrexate. The use of anakinra in combination with other potent immune-modulating drugs is not recommended.
- Possible loss of confidentiality
- Possibility of becoming upset when asked questions about pericarditis

- Allergic reaction to Anakinra is possible. Severe allergic reactions can be life threatening. Please contact your study doctor or seek immediate medical attention if you experience skin rash, swelling, or difficulty breathing as these may be signs of allergic reaction.
- There may be risks associated with this treatment which are unforeseeable.

As the study procedures might injure an unborn child, pregnant women may not participate. Women who might become pregnant should use a medically accepted form of birth control such as total abstinence, birth control pills, an IUD, diaphragm, progesterone injections or implants, or condoms plus a spermicide. Methods of birth control other than total abstinence are not 100% effective, and should a women become pregnant there is a risk of injury to an unborn child. For similar reasons, women who are nursing may not participate. For men, the study procedures might increase the risks for birth defects of any child conceived during treatment and several months after treatment is stopped. Men in this study who have the potential of fathering children should be aware of this possibility and should use a medically accepted form of birth control. A pregnancy test will be performed by the primary clinical team. The results of this test will be provided to the patient (and the patient's family if patient is under the age of 18) by the primary clinical team.

Only the study participant can take the study drug. It must be kept out of the reach of children and persons who may not be able to read or understand the label.

Additional risks related to procedures:

- The potential risks of a blood draw include discomfort, bruising and rarely infection.
- There are no known adverse effects of an EKG.
- During the echocardiogram, you may experience pressure from the probe.

USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

Authority to Request Protected Health Information

The following people and/or groups may request my Protected Health Information:

- Principal Investigator and Research Staff
- Research Collaborators
- Data Safety Monitoring Boards
- Others as Required by Law
- Study Sponsor
- Institutional Review Boards
- Government/Health Agencies

Authority to Release Protected Health Information

The VCU Health System (VCUHS) may release the information identified in this authorization from my medical records and provide this information to:

- Health Care Providers at VCUHS
- Study Sponsor
- Data Coordinators
- Data Safety Monitoring Boards
- Others as Required by Law
- Principal Investigator and Research Staff
- Research Collaborators
- Institutional Review Boards
- Government/Health Agencies

Once your health information has been disclosed to anyone outside of this study, the information may no longer be protected under this authorization.

Type of Information that may be Released

The following types of information may be used for the conduct of this research:

☒ Complete health record

Expiration of This Authorization

☒ This authorization will expire when the research study is closed, or there is no need to review, analyze and consider the data generated by the research project, whichever is later.

Right to Revoke Authorization and Re-disclosure

You may change your mind and revoke (take back) the right to use your protected health information at any time. Even if you revoke this Authorization, the researchers may still use or disclose health information they have already collected about you for this study. If you revoke this Authorization you may no longer be allowed to participate in the research study. To revoke this Authorization, you must write to the Principal Investigator.

BENEFITS TO YOU AND OTHERS

Based on prior reports in patients with severe forms of acute pericarditis, we expect that Anakinra will help to treat inflammation and improve your pain. There is no guarantee however that Anakinra will be effective as tested and as such you may not receive any medical benefit from being in this study. If Anakinra is found to be helpful to control pain due to acute pericarditis, this may be beneficial for other future patients with acute pericarditis. Although less likely, it is also possible that Anakinra is not effective in treating acute pericarditis or that can even make the condition worse, in which case the study doctor, your doctor or you can choose to stop treatment at any time and opt for the standard treatment.

COSTS

You will not be charged for the costs of the study drug or any procedures related to the study. The costs of procedures that are performed as part of standard of care will be billed to your insurance.

PAYMENT FOR PARTICIPATION

You will receive compensation for participation in this study to help offset any costs related to travel, time off from work, etc. You will receive $100 after the first 24 hours, another $100 after the visit on day 7 and another $100 on your last visit on day 30.

ALTERNATIVE TREATMENT

You do not have to participate in this study to be treated for acute pericarditis at this institution. If you decide not to enter this study, there are other treatments available. These include non-steroidal anti-inflammatory drugs (NSAIDs such as aspirin, ibuprofen) and colchicine (also known as Colcrys). Anakinra is not available as a treatment for acute pericarditis outside of participation in this study. Ask the study doctor about these options if interested. You will be informed of any new findings that may relate to your willingness to continue in the research study.

CONFIDENTIALITY

Potentially identifiable information about you will consist of blood work, EKG results, echocardiogram results, and pain assessment answers. Your data will be identified by ID numbers, not names, and stored separately from medical records in a locked research area. All personal identifying information will be kept in password-protected files and these files will be deleted after the study has finished. Access to research data will be limited to study personnel, the Food and Drug Administration as required by law and the sponsor (SOBI). SOBI will only

have access to de-identified data that cannot be connected back to you. Although results of this research may be presented at meetings or in publications, identifiable personal information pertaining to participants will not be disclosed.
It will be noted in your protected electronic medical record at VCU Health System that you are in this clinical trial. Information about the study including any medications you may receive will be noted in the record. This information is protected just as any of your other medical records are protected.
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 Website will include a summary of the results. You can search this Web site at anytime.
VCU is required by federal law to collect your social security number. Your social security number will be kept confidential and will only be used to process payment.

COMPENSATION FOR INJURY or ILLNESS
If you are injured by, or become ill, from participating in this study, please contact your study doctor immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed.
Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study. To help avoid research-related injury or illness it is very important to follow all study directions.

VOLUNTARY PARTICIPATION AND WITHDRAWAL
Your participation in this study is voluntary. You may decide to not participate in this study. Your decision not to take part will involve no penalty or loss of benefits to which you are otherwise entitled. If you do participate, you may freely withdraw from the study at any time and opt for the standard treatment for acute pericarditis. Your decision to with draw will involve no penalty or loss of benefits to which you are otherwise entitled. Your participation in this study may be stopped at any time by the study doctor without your consent. The reasons might include:

- the study doctor thinks it necessary for your health or safety;
- you have not followed study instructions;
- administrative reasons require your withdrawal.

QUESTIONS
If you have any questions, complaints, or concerns about your participation in this research, contact:

Antonio Abbate, MD, PhD
Virginia Commonwealth University
West Hospital, 5th floor, Rm 520
Richmond, VA 23298
(804) 828-0951 (pager 1507)

The researcher/study staff named above is the best person(s) to call for questions about your participation in this study. If you have general questions about your rights as a participant in

this or any other research, you may contact:

Office of Research, Virginia Commonwealth University
800 East Leigh Street, Suite 3000, P.O. Box 980568
Richmond, VA 23298
Telephone: (804) 827-2157

Contact this number to ask general questions, to obtain information or offer input, and to express concerns or complaints about research. You may also call this number if you cannot reach the research team or if you wish to talk to someone else. General information about participation in research studies can also be found at http://www.research.vcu.edu/irb/volunteers.htm.
Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

CONSENT

I have been provided with an opportunity to read this consent form (composed of 8 pages) carefully. All of the questions that I wish to raise concerning this study have been answered. By signing this consent form, I have not waived any of the legal rights or benefits, to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will receive a copy of the consent form once I have agreed to participate.

_____

Participant Name, printed

_____ _____

Participant Signature Date

_____

(if applicable) Name of Parent or Legal Guardian, printed

_____ _____

(if applicable) Parent or Legal Guardian Signature Date

_____

(OPTIONAL) Name of Parent or Legal Guardian, printed

_____ _____

(OPTIONAL) Parent or Legal Guardian Signature Date

_____ _____

Witness Signature Date

_____

Name of Person Conducting Informed Consent Discussion (Printed)

_____ _____

Signature of Person Conducting Informed Consent Discussion Date

_____ _____

Principal Investigator Signature (if different from above) Date