INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0233 PRINCIPAL INVESTIGATOR: Robert Yarchoan, MD

STUDY TITLE: Pilot Study of Tocilizumab in Patients with Symptomatic Kaposi Sarcoma Herpesvirus (KSHV) - associated Multicentric Castleman Disease

Continuing Review Approved by the IRB on 11/13/19
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Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

This is a research study to gain information about a medication called tocilizumab when used to treat KSHV-associated multicentric Castleman disease (KSHV-MCD). KSHV stands for the Kaposi's sarcoma herpes virus, and is also called human herpes virus-8, or HHV-8. In addition to causing KSHV-MCD, KSHV can cause several other tumors, including Kaposi sarcoma and a rare lymphoma called primary effusion lymphoma. Patients with KSHV-MCD often have symptoms including fever, sweats, weight loss, fluid in the legs or abdomen, cough, stomach upset, loss of muscle, and poorly tolerate certain medications. They also have several common blood abnormalities such as anemia, low platelets, and evidence of inflammation. People with

symptomatic MCD have very high levels of a protein called interleukin-6 (IL-6) that leads to some of these symptoms and blood abnormalities. Additionally, the virus makes several proteins, such as a viral form of IL-6, that are also important in causing the symptoms of KSHV-associated MCD. The purpose of the research is to see if the medication, tocilizumab, which is a biologic agent that targets the receptor on cells for IL-6, leads to improvement in KSHV-MCD symptoms and blood abnormalities. Tocilizumab has previously been found to be effective in patients with a form of MCD not associated with KSHV and that is largely caused by human IL-6. It is also FDA approved (brand name Actemra™) for use in patients with rheumatoid arthritis. While tocilizumab does not directly block the action of viral IL-6, there is evidence that human IL-6 may be causing many of the symptoms in patients with KSHV-MCD. Moreover, it is possible that by blocking the receptor of human IL-6, tocilizumab may lower the production of viral IL-6.

If you do not have enough improvement in symptoms and blood abnormalities with tocilizumab alone, you may also be treated with additional medications that target certain cells infected with KSHV. These medications, zidovudine (otherwise known as AZT) and valganciclovir, when combined in the treatment of MCD are sometimes called "virus-activated cytotoxic therapy". It may be that for some people with KSHV-MCD, tocilizumab may be more active in combination with "virus-activated cytotoxic therapy", and this study will gather information on this combination in some patient-volunteers.

Why are you being asked to take part in this study?

Individuals may be eligible to participate in the research study if they have biopsy proven KSHV-MCD, and have symptoms and certain blood abnormalities due to their KSHV-MCD. To be eligible for the trial, patient-volunteers must meet a number of other criteria to make sure that it is appropriate to participate in the study. If you meet these criteria, you are being asked to take part in this study so that we may evaluate tocilizumab alone, or in some patient-volunteers, in combination with "virus-activated cytotoxic therapy" using zidovudine and valganciclovir. Patient-volunteers with HIV must agree to a regimen of combination highly active antiretroviral therapy (HAART).

How many people will take part in this study?

We plan to enroll up to 17 patient-volunteers in this study.

Before you begin the study

HIV Testing

As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will still be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

Description of Research Study

If you consent to participate in this study, you will receive therapy through a vein (IV) every 2 weeks for up to 12 weeks. We will follow you for 4 weeks after you complete your sixth dose of tocilizumab to check for possible side effects of the drug and to make sure your KSHV-MCD does not worsen once therapy is stopped. If your KSHV-MCD worsens during the course of your participation in the study, or does not show significant improvement, you will be offered to continue tocilizumab in combination with "virus-activated cytotoxic therapy" using zidovudine and valganciclovir. Zidovudine and valganciclovir are provided as pills that are taken 4 times a day for 5 days out of every 2 weeks.

During the first week of therapy, we will be taking daily blood samples for three days to see if tocilizumab has an effect on the levels of certain HAART drugs in your blood. We will also be collecting blood, urine and saliva throughout the study for monitoring your health as well as for other research purposes. A description of what will happen if you take part in this study and a list of potential risks and discomforts associated with participation in the study are listed below.

What will happen if you take part in this research study?

Before you begin the study, you will be evaluated by a physician investigator, as well as other members of the research team for eligibility in the study. We will discuss your medical history in detail and will also perform a skin test to determine whether you have been exposed to tuberculosis in the past. A biopsy is required for participation. If you have already had a biopsy, we will work with you to have the biopsy sent to pathologists at the NCI for review. If you have not have not had a biopsy, we will arrange for a biopsy to confirm the diagnosis of KSHV-MCD. You will have a CT scan to evaluate the abnormalities commonly seen in KSHV-MCD, such as large lymph nodes and large spleen. You will also have an 18[F]FDG-PET-CT scan to make sure that you do not have lymphoma. If you also have Kaposi sarcoma, additional measurements and photographs will be performed to document the extent of KS, in some patients, additional studies to evaluate the extent of KS may be required, and a physician will discuss this with you.

During the study, you will receive a tocilizumab every 2 weeks for a total of 6 doses. Patients with HIV will be required to take HAART. Patients with a positive tuberculosis skin test will be required to take a medicine to prevent tuberculosis while on the study if you have not already completed a course of antibiotics for tuberculosis. During the first cycle, you will be evaluated by a physician prior to therapy, and you will have blood drawn daily for the first three days. On subsequent cycles, a physician will evaluate you on the day you receive therapy. If during this evaluation, it is determined that your response to tocilizumab is inadequate, you will be offered "virus-activated cytotoxic therapy" using zidovudine and valganciclovir. Zidovudine and valganciclovir are provided as pills that are taken 4 times a day starting on the day you receive tocilizumab and continuing for 5 days. Examples of reasons that "virus-activated cytotoxic

therapy" may be required including worsening of symptoms and/or blood work due to KSHV-MCD anytime while on study, lack of any sign of improvement in KSHV-MCD after 4 weeks, or lack of evidence of substantial improvement after 8 weeks of tocilizumab.

During each cycle, approximately 10 teaspoons of blood will be collected from a vein to be used for laboratory studies that are part of routine care for patients receiving therapy, as well as special research studies. Saliva and urine will be collected during each cycle. If you have KS your KS will be re-measured and photographed on the day of your fourth dose of tocilizumab and at the end of the study. If your KS completely disappears, you will be asked to repeat any abnormal tests that you had when you entered the study, and this may include a skin biopsy.

After you are finished taking the drugs, we will follow you in clinic 4 weeks later to make sure that you do not have any side effects from the drugs, and to make sure that your KSHV-MCD is not worse after discontinuing the medications.

Your specimens and data may be used to evaluate genetic changes in genes involved in drug-metabolism. Using a commercially available test called the DMET™, NCI investigators can evaluate DNA from your blood cells for approximately 225 genes that are involved in the way your body processes medications. These genes may be involved in the way your body handles some of your HIV medications. NIH researchers are interested in studying these genes, in a preliminary way, in patient-volunteers with KSHV-MCD who receive tocilizumab. The investigators conducting this study do not plan to provide you or your family with the results of any of the research tests or evaluations because at this time this information is not clinically meaningful and further research is necessary before these results may be clinically relevant. Once your samples are received, they are bar-coded and your name removed from the label. Your data will be entered into a computer database. However, patient-volunteers will not be personally identifiable by the scientists who perform the DNA tests. Your medical care will, in no way, be affected by your decision on whether or not you participate in this part of the study. You understand that personal possession of information about your genes could result in discrimination. However, you will receive no results of laboratory analysis of your sample, nor will these results become part of your medical record, as the results will be preliminary in nature. As a consequence of this, you will not be placed in the position of having information about your genes that you may not wish to reveal to others. Your research blood will not be used for clinically relevant genetic testing. As such, participation in this result will not obligate you to state that you have received genetic testing. In addition, your family will not have access to this investigational information. You will be given the opportunity to decide whether you would like to participate in this testing.

The following Study Chart outlines what will happen if you choose to participate.

Screening for Eligibility

- Medical History and Physical Exam
- Review of Biopsy
- Blood and Urine Studies
- 18[F]FDG-PET scan
- CT scan
- Tuberculosis skin test

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Treatment

Tocilizumab:	IV tocilizumab every 2 weeks for 6 cycles
Addition of zidovudine and valganciclovir:	Added if: • Worsening KSHV-MCD with tocilizumab alone OR • No evidence of improvement after 4 weeks OR • No substantial improvement after 8 weeks AZT is two tablets every 6 hours for 5 days, valganciclovir is 2 tablets every 12 hours for 5 days
Monitoring:	Review of side effects Physical Exam, Blood Samples KS measurements and photography (in patients with KS)
Research:	Cycle 1 only (in patients with HIV), blood samples on days 1, 2, and 3 to measure levels of antiretroviral drugs Each cycle: Blood, urine and saliva samples
Stop treatment:	Completion of 6 cycles of tocilizumab Progressive KSHV-MCD that does not improve despite addition of zidovudine and valgancyclovir Patient preference

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After treatment

- Clinic visit 4 weeks after completing therapy
- Research blood and saliva samples
- Long-term follow up may be possible under other KSHV-MCD protocols

Standard of Care Treatment:

Treatments required for those participating in the study may include standard medications. For example, patient-volunteers who are HIV positive must agree to take combination antiretroviral therapy. If you take zidovudine as part of your participation on the study, your antiretroviral therapy may be adjusted during the weeks you take zidovudine, as zidovudine is an antiretroviral drug. Those who have a positive tuberculosis skin test will be prescribed medicine to prevent tuberculosis based on national guidelines. These treatments will not be experimental. Your doctors will describe your treatment plan to you in detail before asking you to sign this consent form. Furthermore, participation in the study may include additional procedures to document the extent of KS in your case. In such a case, you may be asked to sign a separate consent form for any additional treatment procedures not outlined in this consent.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 3 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy
- barrier methods [condoms]

Risks or Discomforts of Participation

What side effects or risks can I expect from tocilizumab?

Likely (10% or greater incidence)

- Discomfort from blood draws, catheter placement or biopsies

Less Likely (less than 10% incidence)

- Infections, mainly respiratory tract infections such as sinusitis or bronchitis
- Sore throat
- Abnormal liver tests
- Headache
- Cough

- Hoarseness
- Dizziness
- Stomach discomfort
- Elevated blood pressure
- Rash
- Decrease in white blood cells or platelets
- Elevated cholesterol

Rare but Serious

- Gastrointestinal perforation
- Life threatening allergic reactions
- Development of a second cancer

What side effects or risks can I expect from "virus-activated cytoxic therapy" using zidovudine and valganciclovir?

High Dose Zidovudine + Valganciclovir: Zidovudine, also called Retrovir™. This medication is approved by the FDA to treat HIV infection. In this study, the dose is considerably higher than what is used to treat HIV. The zidovudine dose in this study is up to 4 times the standard dose used in HIV infection. It is given either as oral medication or through a vein, 4 times daily. Valganciclovir, also called Valcyte™, is approved for the treatment of CMV infection. The doses used in this research study are similar to the doses used in CMV infection, but the schedule is different. Potential side effects of the combination include:

Likely:

- Gastrointestinal distress which is usually worst when starting the medication
- Loss of appetite.
- Abnormal taste.
- Diarrhea.
- Headache.
- Difficulty sleeping.
- Dizziness.
- Weakness and fatigue.
- Fingernail changes.
- Anemia (low red blood cell counts).

Less likely:

- Nausea and vomiting.
- Abdominal pain.
- Low white blood cell counts. If white cell counts become very low, this will increase your risk for infections.
- Low platelet counts. If platelet counts are very low, you are at increased risk of bleeding. If the platelet count is very low, you may need a platelet

transfusion
- Tingling of fingers and/or toes.
- High blood sugar levels.
- Changes in vision due to damage to your retina.

Rare, But Serious:
- Liver damage.
- Muscle damage.
- Lactic acidosis, which a build-up of acid in your blood. The signs of lactic acidosis are deep and rapid breathing, vomiting, and abdominal pain.
- Defects to the developing fetus.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if tocilizumab alone (or in some cases, combined with zidovudine and valganciclovir) provides you with direct clinical benefit. Potential benefits include partial or complete improvement of all symptoms or lab abnormalities that are due to your KSHV-MCD. We hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. For patients with KS, we will be closely monitoring your KS, as the effect of tocilizumab on KS is unknown, but could potentially be beneficial, especially compared to rituximab, another drug used to treat KSHV-MCD, that frequently (in about 30-40% of patients) can lead to improvement in KSHV-MCD but a worsening of KS. We cannot predict whether you will benefit directly from taking part in this study, although the knowledge gained from this study may help others in the future who have KSHV-associated cancers.

Alternative Approaches or Treatments

KSHV-MCD is a rare disorder, and there are no FDA approved therapy options for the management of this disease. Off-label use of several anti-viral drugs, biologic agents, and chemotherapy drugs has been shown to have activity in small studies performed by our group and others. There are several alternative approaches available at the NCI under a separate protocol, including "virus-activated cytotoxic therapy" without tocilizumab, or rituximab combined with liposomal doxorubicin. Your physician will talk to you about these options, and the risks and benefits of these or other alternative approaches that might be offered outside of this clinical study. Generally, patients with symptomatic KSHV-MCD have a progressive course of waxing and waning symptoms that is associated with a high risk of developing lymphoma and/or death, so observation is without therapy is generally not considered a viable option.

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options**:**

- Getting treatment or care for your KSHV-MCD without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to the NCI, FDA or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you

by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.

- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

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.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using tocilizumab, zidovudine, and valganciclovir in investigator-initiated research. This means that the drug companies that make these drugs are not sponsoring this study. One of the investigators on this study is the co-inventor on a patent describing the measurement of KSHV vIL-6. This invention was made while the investigator was employee of the US Government under 45 Code of Federal Regulations Part 7. All rights, title, and interest to this patent have been assigned to the U.S. Department of Health and Human Services. The government conveys a portion of the royalties it receives to its employee inventors under the Federal Technology Transfer Act of 1986 (P.L. 99-502). It is possible that the results of this study could lead to payments to NIH scientists and to the NIH. By law, government scientists are required to receive such payments for their inventions. You will not receive any money from the development of tocilizumab or of the blood test for vIL-6.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Robert Yarchoan, M.D., Building 10, Room 6N106, Telephone: 240-760-6075. You may also want to contact the lead research nurse, Ms. Anaida Widell at 240-760-6074. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM NOVEMBER 13, 2019 THROUGH DECEMBER 03, 2020.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____