Protocol Title: Rituximab (Anti-CD20) for the Treatment of Subjects with Anticytokine Autoantibody-Associated Diseases

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STUDY SITE: National Institutes of Health, Clinical Center

Cohort: Adult

Consent Version: 02/25/2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Christa Zerbe, MD, 301-594-5932, zerbech@niaid.nih.gov

Study Coordinator: Christine Lafeer, RN, BSN, 301-761-6902, clafeer@niaid.nih.gov

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

You are being asked to take part in this study because you have an anti-cytokine autoantibody-associated disease. Healthy people make antibodies to protect them against foreign material, such as bacteria, viruses, and fungi. People with diseases like yours make antibodies that attack their own proteins. Anti-cytokine autoantibody-associated diseases lead to severe infections and severe lung disease or other complications, and even death, even with treatment with standard medications.

The purpose of this study is to see how well rituximab is tolerated by people with anti-cytokine autoantibody-associated diseases and to see if the drug works to treat these diseases. Rituximab is a drug approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis in combination with another drug (methotrexate) and for non-Hodgkin's lymphoma.

Rituximab has not been approved for the treatment of anti-cytokine autoantibody-associated diseases. We have received permission from the FDA to use rituximab for this study.

A small number of people with diseases like yours have done well with rituximab. Six people with anti-cytokine autoantibody-associated diseases were treated with rituximab by our study staff with rituximab. All 6 subjects got better without any serious side effects. Half of them had side effects related to receiving rituximab through a vein in their arm.

The prescribing information from the manufacturer of this drug states that "rituximab is not recommended for use in patients with severe, active infections." But we feel that rituximab can help treat the cause of your infection—the autoantibodies that attack your proteins. Also, rituximab is not likely to make the type of infection you have worse.

STUDY SCHEDULE

Your study participation time will be around 24 months. You will receive at least 2 doses of rituximab. You will be followed monthly for the next five months. Then you will have follow-up visits for the rest of the 18 months, every 3 months after your last dose of rituximab. You will be given a schedule with the dates for your return visits. The study doctor will let you know if you need to return to NIH for more follow-up visits after the 18 months.

Screening evaluation visit

If you have been screened on a separate protocol within 90 days of the start of this study, you will ***NOT*** need to undergo the following tests. We will only repeat tests if they were done more than 90 days from the start of the study.

- **Physical exam/medical & medication history:** We will ask you for your medical and medication history will be collected, and you will have a medical exam.
- **Blood tests:** Blood will be drawn from a vein in your arm to measure your blood cell counts, to see if your organs, like your liver and kidneys, are working well, and to check markers of your disease. Your blood will also be used to test for the human immunodeficiency virus (HIV), the virus that causes AIDS, and for hepatitis B and C, which cause liver disease. The total amount of blood drawn during the study visits is around 5 to 6 tablespoons. This is within the amount allowed to be drawn for research blood draws in adult subjects at the NIH Clinical Center. While in the study, let the study team know if you are participating in other studies or have blood drawn for any other reason.
- **Pregnancy test:** If you are a woman of childbearing age, your blood will be tested to see if you are pregnant.
- **Urine collection:** A sample will be taken for routine analysis to see if your body is working properly.
- **Microbiology test:** Samples will be taken from infected sites, such as the skin, sputum (mucus/spit out from the lungs), or other sites to test for infection.

Baseline evaluation visit

- The baseline evaluation visit will take place within 24 hours prior to your first dose of rituximab on day 1. The procedures listed under the screening evaluation visit will also be performed at this visit except for the head MRI.
- In addition to the blood draw described under the screening evaluations, about 4 more tablespoons of blood will be drawn from you for research purposes to study the effect of your disease. Also, we may instead ask you to undergo a procedure called apheresis, which will allow us to collect more blood from you to study your disease. If you choose to undergo apheresis, you will be asked to sign a separate informed consent, and you will ***NOT*** need to provide the additional 4 tablespoons of blood. Your decision to undergo apheresis will not affect your participation in the current study.

Study-phase evaluation visit

You will be hospitalized at the NIH Clinical Center for your rituximab doses on day 1 and possibly on day 15.

- **Dosing with rituximab:** Rituximab will be given to you through a vein in your arm (intravenously) on days 1 and 15. The first dose will take approximately 5 hours. The second dose should not take as long. Thirty to 60 minutes before each dose, you will receive Tylenol (acetaminophen; 325 milligrams by mouth), Benadryl (diphenhydramine; 25 to 50 milligrams by intravenous infusion), and possibly Medrol (methylprednisolone; 100 milligrams by intravenous infusion) to help prevent side effects from rituximab dosing.

- **Blood tests:** Blood will be drawn prior to the rituximab dose to measure your blood cell counts, to see if your organs are working well, and for research purposes to study your disease.

Additional 5 months

- **Questionnaire:** You will also be asked to fill out a questionnaire before the first dose and again at the last of your monthly visits. The questionnaire will help us see how you feel about your current state of health and to assess your quality of life.
- **Dosing with rituximab:** You will return every month starting around day 42 for a visit that includes a physical exam, as well as, blood and urine collection, microbiology and pregnancy testing, if you are female. You may receive more doses of rituximab if your symptoms or tests show that you did not improve after the first two doses of rituximab. If you need more doses, you may get those in the day hospital or in the inpatient unit. The medical team will decide where you get the doses depending on how well you did with your other doses. Each dose will take about 2 hours. Thirty to 60 minutes before each dose, you will receive Tylenol, Benadryl, and possibly Medrol to help prevent side effects related to rituximab dosing. Your disease progress will be watched throughout the study to see if you need to be treated with more rituximab.

Follow-up evaluations

- You will return to the NIH for 6 more follow-up visits at 3, 6, 9, 12,15, and 18 months after the last dose. The study doctor will let you know if you need to return more often.

- The procedures listed under the screening evaluations visit will also be done at these visits. Also, blood will be drawn from you for research purposes to study your disease.

RISKS ASSOCIATED WITH THE STUDY

- **Rituximab:** More than 2.7 million people have received rituximab to date. Because rituximab can result in severe side effects, you will receive Tylenol, Benadryl, and possibly Medrol before each rituximab dose. Also, you will be admitted to the hospital for the first dose and possibly the second dose, so that we can watch you closely.

  Here is a list of side effects related to rituximab:

  - ✓Infusion reactions, such as fever, chills, nausea/vomiting, severe itching, skin allergy, headache, weakness, wheezing, dizziness, low or high blood pressure, throat irritation, and muscle pain. These side effects generally occur within 30 to 120 minutes after the start of the dose. They usually resolve if the drug is given at a slower rate or stopped. Death has also been reported within 24 hours after infusion with rituximab.
  - ✓Tumor lysis syndrome (TLS) has been seen in some subjects with a certain type of cancer after treatment with rituximab. TLS occurs when tumor cells die quickly and release toxic break-down products into the bloodstream. Symptoms can include nausea, vomiting, diarrhea, lack of appetite, lack of energy, blood in the urine, heart problems, convulsions, muscle cramps, and others. TLS is unlikely to occur in the current study since patients with cancer are not asked to participate.
  - ✓Severe skin and mouth reactions, such as the Stevens-Johnson syndrome, have been reported at 1 to 13 weeks after rituximab dosing. Stevens-Johnson syndrome is associated with swelling of the face and tongue, hives, skin pain, skin rash/sloughing, and blisters on the skin, nose, and eyes. Some of these severe reactions can result in death.
  - ✓Progressive multifocal leukoencephalopathy (PML) has been reported in less than 1 in 10,000 people treated with rituximab. PML is a rare and usually fatal disease caused by the JC virus, which results in brain damage. In healthy people, the immune system fights off the virus, but weakening of the immune system prevents it from controlling the virus.
  - ✓Effects on fertility and unborn children: Because the risks of rituximab are unknown in unborn children, pregnant or nursing women will not be allowed to participate in this study. Men capable of fathering a child and women of childbearing potential must agree to use 2 acceptable methods of contraception (such as birth control pills, male/female condoms with or without spermicide, diaphragm or cervical cap with spermicide, or intrauterine device) before and during the study and for 18 months following the last dose of rituximab. If you are a woman of childbearing potential, you must have negative pregnancy test results. If you are a woman who could become pregnant, you will have to agree to notify the study doctor immediately if you suspect or know that you are pregnant while on the study. If you become pregnant, you will be withdrawn from the study for your safety and the safety of your unborn child.
  - ✓Other potentially life-threatening side effects include reinfection with the hepatitis B virus, serious infections, heart problems, kidney failure, low blood cell counts, blockage and piercing of the gut, and allergic reactions.

- ✓ In addition to the risks listed above, other unexpected risks may occur that we have not yet seen with this drug.

- **Benadryl and Medrol:**
  - ✓ Benadryl might cause drowsiness; dizziness; dry mouth, nose, and throat; nausea; vomiting; loss of appetite; constipation; increased chest congestion; headache; muscle weakness; and nervousness.
  - ✓ Medrol might cause salt retention, heart failure, high blood pressure, fluid retention, potassium loss/low levels, muscle weakness, loss of muscle mass, brittle bone disease, spine/bone fractures, bone death, sore lining of your stomach/small intestine, inflammation of the pancreas or swallowing tube, swollen abdomen, wounds that don't heal, skin bruising/fragile skin, reactions to skin tests, face redness, increased sweating, increased skull pressure, seizures, dizziness, headache, abnormal secretion of steroids, irregular periods, decreased use of carbohydrates by the body, diabetes symptoms, increased use of insulin/other agents in diabetics, clouding of the eye lens, increased eye pressure, eye disease, eye bulging, nitrogen imbalance, itching or other allergic reactions.
- **Blood draws and drug infusion:** The risks associated with drawing blood from a vein in your arm, or infusing the study drug into the vein, include pain, bruising, and, rarely, infection at the site, hematoma or black and blue mark with a lump caused by blood release into the tissues, lightheadedness, and fainting.
- **HIV testing:** If you are infected with HIV, you will not be able to participate in this study. The study team will tell you what the results mean, counsel you, and refer you to a local clinic for care and treatment. Your HIV test results will be included in your medical record and our study records. To the extent permitted by the law, your information will not be disclosed to other individuals. However, certain national laws can require us to disclose information from your study records to legally authorized individuals. The study staff cannot control how this information is used. All of the study information under our control will be kept strictly confidential in locked files at the NIH. If you have any questions regarding the HIV testing, or the information provided in this consent, you are encouraged to discuss them with the study doctor.
- **Unanticipated medical information:** There is a possibility that results from the tests performed in this study will lead to a new or future diagnosis for a disease that you did not know you had. This news may be stressful for some people. If your test results show a new or future diagnosis for a disease, this information will be shared with you and your primary doctor at your request. You will also be referred to your primary doctor for further evaluations and treatment.
- **Genetic testing:** Genetic tests may be performed in the future on your stored samples to help us better understand autoimmune diseases. Genetic tests done in a research laboratory from your stored samples will not become part of your medical record, and the tests will not include your name.

Some genetic tests are done in a regular medical laboratory. HLA type is a genetic test that may be ordered through the NIH Clinical Center medical laboratory. If performed, your HLA type results will become part of your medical record at the NIH Clinical Center.

There is a new type of gene test that lets us look at all the genes at once, called whole exome or whole genome sequencing (WGS). This test lets us look at every gene in someone that could be part of getting infections or immune problems. Whole genome sequencing provides raw data on all six billion letters in an individual's DNA. However, it does not provide an analysis of what that data means or how that data can be utilized in various clinical applications, such as in medicine to help prevent disease.

- **Genetic data sharing:** Following genetic testing for whole genome sequencing, your sequence data will be shared in a controlled access public database so other investigators may also benefit from it (for example, the Database of Genotypes and Phenotypes, dbGaP). Your genotype is your collection of genes. The expression of your genotype contributes to your observable traits, called the phenotype, such as height, eye color, and blood type. Some traits are largely determined by the genotype, while other traits are largely determined by environmental factors. No personal, identifiable information will be shared in this process, as shared results will be coded with no link back to you. It is possible, however, that someone with a high level of expertise could link anonymous data stored in such a database with an individual person.

  The performance of these tests is not for health care purposes; however, if a genetic research test reveals information about you that is clearly important to your health, the study doctor will attempt to contact you. Since these tests are being performed after the study is completed, you should make certain that the study team knows how to contact you in the future.

BENEFITS ASSOCIATED WITH THE STUDY

You may benefit from the current study if you don't respond well or can't tolerate the standard therapy currently available for the treatment of your disease.

ALTERNATIVES TO PARTICIPATING IN THE STUDY

You may choose not to participate in this study and continue to receive care from your current physician(s).

STOPPING PARTICIPATION

You can stop participating in this study at any time. Tell a member of the study team if you no longer want to participate. This decision will not affect your ability to receive care at the Clinical Center. Blood and tissue samples and data collected prior to this request will be stored for the duration of the protocol unless you specifically request the removal of all your samples from the study.

EARLY WITHDRAWAL

You may be removed from this study without your consent for the following reasons:

- The study doctor feels that staying in the study would be harmful to you.
- The study is stopped or cancelled.
- You become pregnant.
- You don't keep your appointments or refuse to undergo study procedures as required.
- You are not compliant with study requirements.

NEW FINDINGS

Any new findings discovered during this study that are considered relevant to your health will be fully discussed with you.

CONFLICT OF INTEREST

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

No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested.

PAYMENT

Will you receive any type of payment for taking part in this study?

You will not receive any payment for taking part in this study.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

If your travel to the NIH Clinical Center (e.g., flight, hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

The costs for any other medical care provided outside the NIH during this period will not be covered.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

If you agree to participate in this study, you also agree to let us store your blood samples and data for future research. If tissue biopsies are collected from you during any of the procedures for medical reasons, samples of such tissue may be stored for future research studies. The stored samples/data may help us learn more about autoimmune diseases, and cell samples collected from you might be used for the development of biological therapeutics. The samples/data will be labeled with a code that only the study team can link to you. Any information that can be traced back to you will be kept as private as possible. Additional genetic testing may also be performed in the future on your stored samples. If you change your mind and decide you do not want us to store your samples, please contact us. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy all your samples.

Your coded samples/data might be sent to other study doctors for their research. Other information, such as your sex, age, health history, or ethnicity might also be shared. Your samples will not be sold, and you will not be paid for any products that result from this research. Future studies may require health information about you, such as smoking history or present health status, which we don't already have. If so, our study team will contact you. Future research that uses your samples/data will not help you, but it may help us learn more about autoimmune diseases and other health problems. In general, the research tests performed in this study are not like routine medical tests, and they may not relate directly to your medical care.

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 NIH 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

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH 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 NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

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, Christa Zerbe, MD, zerbech@niaid.nih.gov, 301-594-5932. Other researchers you may call are Christine Lafeer, RN, BSN, at 301-761-6902. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.