INSTITUTE: National Eye Institute

STUDY NUMBER: 11-EI-0263

PRINCIPAL INVESTIGATOR: Catherine Cukras, MD, PhD

STUDY TITLE: A Pilot Study for the Evaluation of Minocycline as a Microglia Inhibitor in the Treatment of Branch Retinal Vein Occlusions

Continuing Review Approved by the IRB on 01/16/19
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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.

1) Why is this research being done?

The purpose of this study is to see if a drug, minocycline, can help patients with Branch Retinal Vein Occlusion (BRVO).

BRVO often leads to macular edema, a swelling of the retina in the back of the eye that is a common source of vision loss. Studies have suggested that inflammation might be a cause. Thus, if it can be controlled, vision may be kept intact.

Minocycline is a drug that might help prevent cells involved in inflammation from becoming activated. If it can, it might help treat macular edema.

Minocycline is approved by the FDA as an antibiotic. Minocycline has not been studied before to see if it can help alleviate the effects of BRVO. Those who participate in this study will be given either minocycline or placebo. A placebo is a harmless sugar pill that will have no effect. Neither you nor your study doctors will choose or know whether you are taking minocycline or placebo. Whether you receive minocycline or placebo will be chosen at random – like rolling dice. The type of pill you take will stay the same throughout the study. The FDA has approved the experimental use of minocycline for this study.

2) Why are you being invited to participate?

You have been asked to participate in this study because you have BRVOs in at least one eye. We will choose the affected eye as the "study eye".

To be eligible for this study, you must:

- Be 18 years of age or older.
- Be able to understand and sign this consent form for yourself.
- Agree to inform us if you start a new medication while you are in this study.
- Agree to protect yourself from sunlight or artificial UV rays while in this study.
- Have vision between 20/32 and 20/200 in the study eye.

- Not be pregnant. If you are a woman who is able to get pregnant or if you are a man able to father children, you (or your partner) must have had a hysterectomy or a vasectomy, be completely abstinent from intercourse or be willing to use two effective methods of birth control while in this study and for one week after you stop taking the study pills.

  Please be aware that minocycline can make hormonal contraceptives less effective and thus increase the risk of pregnancy. Acceptable methods of birth control for this study include the combined use of TWO of the following methods:

  1. hormonal contraception (birth control pills, injected hormones, skin patch or vaginal ring),
  2. intrauterine device
  3. diaphragm with spermicide or a condom with spermicide
  4. tubal ligation.

You cannot participate in this study if:

- You have had BRVOs in your study eye for longer than 18 months.
- You are in another research study and are taking investigational study drugs for BRVO.
- You are allergic to the dye used for fluorescein angiography.
- You are allergic to minocycline or any drug in the tetracycline family.
- You have any illness or condition that might make it unsafe for you to participate, such as high blood pressure that is not controlled with medicine.
- You have a history of chronic hepatitis or liver failure.
- You are currently taking a tetracycline medication.
- You are taking systemic anti-VEGF medication such as Avastin® (bevacizumab) or systemic steroids.
- You have had thyroid cancer.

- You are taking any medication that is unsafe to take with minocycline, such as methoxyflurane. Methoxyflurane is used for general anesthesia and can cause serious or fatal kidney damage if used with minocycline. **If you need general anesthesia or sedation at any time while you are in this study, please make sure that you inform your doctors that you may be taking minocycline for this study.**

You are not eligible now, but you may be able to enroll at some later date if:

- You have a blood pressure that is above 180/110. If your blood pressure is brought below 180/110 by treatment, you may become eligible for this study.
- You have had eye injections in your study eye within the past 28 days with anti-VEGF agents such as Avastin® (bevacizumab), Lucentis® (ranibizumab) or Macugen® (pegaptanib sodium)
- You had a steroid eye injection within the past three months.
- You had a stroke or heart attack within three months prior to study entry.
- You had photocoagulation in your study eye within four months prior to study entry.
- You had eye surgery in your study eye within six months of study entry.
- You had a YAG treatment in your study eye within two months of study entry

3) How many people will take part in this research study?

Up to twenty participants with BRVO will be enrolled in this study.

4) How long will you take part in this research study?

This study lasts two years (24 months). The study requires at least 25 visits to the NEI outpatient clinic. Each visit will last about three hours.

You will have an initial visit followed by monthly visits for 24 months. You may need to return to the clinic for additional appointments as medically needed.

You will stay under the care of your own doctors for your general medical care while you are in this study. You should tell all of your own doctors about this study and that you may be taking minocycline so that they can avoid drug interactions that might be dangerous.

5) What do we do to decide if you are eligible for this research study?

At your first visit, we will ask you about your medical and eye disease history, perform a physical examination, and examine your eyes. If only one of your eyes has macular edema from BRVO, we will call that the "study eye." If both of your eyes have macular edema from BRVO, we will choose one of your eyes to be the "study eye." We will test your vision and measure the thickness of your retina. We will draw blood by placing a needle in a vein in your arm to test blood count and blood chemistries. If you are a woman who is able to get pregnant, you will have a pregnancy test.

6) What procedures, drugs, or other treatments are involved in this research study?

If you are eligible to participate, you will be assigned to take either minocycline or placebo. The minocycline and placebo pills will look the same. Both the minocycline and placebo pills will be prepared by Pine Pharmaceuticals (Tonawanda, New York). Neither you nor your doctor will know which you are taking. The placebo pills will be made of inactive ingredients and will have no medical effect. You will start taking the study pills, minocycline, or a placebo, the evening after your first study visit. You will take one pill twice a day for two years. You should take one pill in the morning and one pill in the evening, at about the same time each day, about 12 hours apart. You will need to record the morning and evening doses of pills taken in a diary that we will give you.

You will return for an outpatient visit once a month for 24 months. You will need to bring the diary and your pill bottle with any unused study pills with you to each visit. At each visit, we will ask you about your health and what medications you are taking. Please tell us about any changes in your medications that your own doctors may have made.

At each study visit, you will have some or all of the following tests:

Eye Examination: The eye examination includes testing how well you see, measuring your eye pressure and checking your eye movements. To examine the inside of your eyes, we will use eye drops to dilate your pupils. While your eyes are dilated, we will

measure the thickness of your retina. Photographs of the inside of the eyes may be taken during the eye examination and while your eyes are dilated.

Thyroid Gland Examination: We will examine the thyroid gland in your neck. We will feel your thyroid gland while you swallow. If the examination suggests a possible problem with your thyroid gland, you will be referred to an endocrinologist.

Fluorescein Angiography: For fluorescein angiography, an intravenous line will be placed in a vein in your arm. The intravenous line will be used to inject a dye called "fluorescein." The dye will travel through your veins and into the blood vessels in your eyes. A camera will be used to take pictures of the dye as it flows through the blood vessels in your eyes.

Microperimetry: We will test how well you can detect different levels of light. You will be seated in front of a computer screen and asked to press a button when you see a light on the screen.

Blood Tests: Blood will be drawn for blood chemistries, blood cell counts, thyroid tests, and tests of your blood sugar level. Blood will be drawn at several study visits. We will draw no more than ½ cup of blood at one time and no more than five cups of blood during the entire study.

Urine Tests: Women who are able to get pregnant will have a urine pregnancy test.

Eye Injection: You will receive bevacizumab (Avastin®) treatment in your study eye at your baseline, Month 1 and Month 2 visits. You may continue to receive this treatment at later visits if needed.

In this study, bevacizumab is being used for "off-label" use, meaning that the drug has not been FDA-approved for the treatment of macular edema due to retinal vein occlusions. However, bevacizumab is similar in structure to the anti-VEGF drug, ranibizumab, which has FDA-approval for macular edema due to retinal vein occlusions. There are insufficient data at this time to determine definitively if one anti-VEGF drug be preferred over the other in this situation. Because of this, it is standard practice to use either bevacizumab or ranibizumab to treat this condition. At this time, we do not know whether one anti-VEGF is better than the other.

In your third month of taking the study medication, you will be able to get focal laser treatment in your "study eye," if it is needed. You can receive treatment for the non-study eye at the NIH or from your own physician.

7) What are the risks and discomforts of this research study?

Risks of Minocycline: Minocycline is an antibiotic. It is widely used to treat infections. The most common side effects of minocycline are diarrhea, upset stomach or abdominal pain.

Minocycline can make your skin and eyes sensitive to sunlight and can cause dark patches on the skin. Exposure to sunlight, even for brief periods of time, may cause a skin rash, itching, redness or other discoloration of the skin, or severe sunburn. When you take this medicine, you should:

- Wear protective clothing, including a hat and sunglasses whenever you are outside.
- Apply a sun block product that has a skin protection factor (SPF) of at least 15 to your skin and a sun block lipstick to your lips. Some participants may require a product with a higher SPF number, especially if they have a fair complexion.
- Use extra caution near water, snow, and sand because they reflect and intensify the damaging rays of the sun.
- Not use a sunlamp or tanning bed or booth.

You may still be more sensitive to sunlight or sunlamps for two weeks to several months or more after stopping this medicine. If you have a severe reaction, see your doctor immediately.

Light-headedness, dizziness and vertigo have been reported with minocycline.

A potentially fatal reaction called "Drug Rashes with Eosinophilia and Systematic Symptoms (DRESS)" has been reported with minocycline use. You should contact the study team or your own doctors immediately if you develop a new rash.

Some cases of thyroid cancer have been reported in people taking minocycline. We will monitor you for signs of thyroid cancer by examining your thyroid and by blood tests. If needed, we will refer you to an endocrinologist for further evaluation.

Other rare but potentially severe side effects of minocycline include allergic reactions (rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips or tongue), bleeding or discharge from the gums, bloody stools, blurred vision, decreased hearing, fever, headache, inflammation of the pancreas (which can cause stomach tenderness, nausea, vomiting, increased pulse rate), joint pain, muscle pain or weakness, or liver toxicities. We will treat these if they occur.

If you develop side effects, including, but not limited to those listed above, or have to stop taking minocycline for any reason, we ask that you notify us immediately. Even if you stop the minocycline, we ask that you continue to come for the remaining study visits so that we can follow your macular edema.

Minocycline can interfere with helpful bacteria in your body, such as those living in your intestines that help with digestion. Therefore, we recommend including live culture yogurts in your diet or taking probiotic dietary supplements, which can help maintain these bacteria, while you are participating in this study.

CAUTION: MINOCYCLINE CAN HARM A FETUS. Both men and women need to use contraception while in this study.

Minocycline can lower sperm count. We do not know if a child fathered by a man taking minocycline could be affected.

Minocycline can harm a fetus when taken by a pregnant woman. It can cause permanent discoloration of the child's teeth. Minocycline passes into breast milk and can cause permanent discoloration of the teeth of a nursing infant. Therefore, women who are pregnant, nursing, or wishing to become pregnant, cannot participate in this study. Men should avoid fathering a child while in this study.

Women who are able to get pregnant will have a urine pregnancy test done at each study visit. If you or your partner becomes pregnant while participating in this study or suspect that you might be pregnant, you must tell us immediately. The doctor will advise you of the possible risks to your unborn child and options available to you. If you become pregnant, we will stop the minocycline immediately and you will be withdrawn from the study.

Risks of Eye Examination, Dilation and Photography: There is minimal medical risk from the tests of vision, measuring eye pressure and eye photography. During the exam, the eye drops used to dilate your eyes may sting. You may have glare and blurry vision for several hours while your eyes are dilated. Some people are allergic to eye drops, while others experience a temporary increase in eye pressure. Your eye could become red or painful. These problems will be treated if they occur.

Risks of Physical Examination: Please note that this physical examination is for research purposes only and does not replace any examination you may receive from your own physicians.

Risks of Microperimetry and Urine Pregnancy Tests: There are no medical risks from these tests.

Risks of Fluorescein Angiography: The risks of an intravenous catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling. These will be treated if they occur. The dye may cause your skin to turn yellow for several hours. Because the dye passes through your kidneys, your urine will turn dark orange for up to 24 hours after the exam. Some people feel nauseous for a few seconds during the fluorescein angiogram. The fluorescein dye can leak out of your vein during the injection and cause the skin to feel mildly uncomfortable or become yellow. The mild discomfort usually lasts only a few minutes, and the yellow color goes away in a few days. In rare cases, there is an allergic reaction to the dye, which causes a rash and itching. Allergic reactions are treated by antihistamines, given by pills or a shot if needed. Severe allergic reactions that cause difficulty breathing and a drop in blood pressure can be life-threatening but are very rare. This would be treated immediately. Please let your doctors know if you have ever had an allergic reaction to fluorescein.

Risks of Drawing Blood: You may have some discomfort and bruising at the site of needle entry. There is a very small risk of fainting. Infection in the area of the needle insertion is rare.

Risks of Bevacizumab Injection: There are risks related to the eye injection itself. As with any injection in the eye, there is a risk of infection and tears or detachment in the retina at the back of the eye. We will lessen the risk of infection by cleaning your eye prior to injection and using sterile instruments to give you the injection. If you develop

an infection, we will treat you with antibiotics. If you develop a tear in the retina, we will seal the tear with laser. If you develop a retinal detachment, you will require an operation to fix the retina. In previous studies with bevacizumab injection, the chance of developing an infection or retinal tear or detachment was less than 1%. There is a risk of elevated eye pressure which would be treated with eye drops if this occurred. If the pressure does not decrease with eye drops, we may need to drain eye fluid by placing a small needle in the eyeball. Another risk of injections into the eyeball is cataract formation, which may require surgery to treat.

Bevacizumab is given intravenously (IV) for other diseases. When given by IV, side effects of bevacizumab include stroke, high blood pressure, and an irregular heartbeat.

Allergic reactions to bevacizumab can occur but are rare. Allergic reactions may be mild, such as skin rash or hives, or severe, such as breathing difficulties or shock. A severe allergic reaction could result in permanent disability or death and requires immediate medical treatment. If you develop serious symptoms, go to your nearest emergency room immediately. Do not wait to call us.

An uncommon but potentially serious side effect that some patients treated with intravenous bevacizumab have is gastrointestinal (GI) perforation, or a tear in the stomach or intestines. Symptoms of a GI perforation include abdominal pain, nausea, vomiting, constipation and fever.

Intravenous bevacizumab treatment can lead to slow or incomplete wound healing. Bevacizumab can also cause severe bleeding, such as bleeding in the stomach, bleeding in the brain, coughing up blood, vomiting blood, nosebleeds, and vaginal bleeding. If you experience any of the symptoms described here, you should seek immediate medical attention, in our clinic or from your own doctors.

There is a chance your vision may worsen while you are in this study. Worsened vision could occur because of the progression of your eye disease, as a side effect of bevacizumab, or for other reasons.

8) Are there any benefits to you if you take part in this research study?

You may benefit from participating in this study if you receive minocycline and it helps treat macular edema secondary to BRVO. In addition, your participation will help us

learn more about BRVO and macular edema that might help you or others in the future.

9) What other choices do you have?

You may choose not participate in this study but to pursue other therapy under the care of your own physician. Such treatments include laser treatment, or eye injections of steroids, bevacizumab (Avastin®), ranibizumab (Lucentis®), or pegaptanib sodium (Macugen®). Your doctors will discuss these options with you before you enroll in this study.

If you participate, you will be able to receive bevacizumab (Avastin®) eye injections or laser treatment during the study, if you need it.

Minocycline is an FDA-approved antibiotic. You may not have to participate in this study to receive minocycline. Your own doctor may be able to prescribe minocycline for you as an "off-label" use.

10) Are there reasons that your research participation may end early?

You can withdraw from this study at any time without losing any of the benefits to which you may otherwise be entitled. We may remove you from the study if medical problems develop or if you are unable to comply with the requirements of the study. We will remove you from the study if you need to start a medication that cannot be taken safely with minocycline. We will remove you from the study if you require a treatment that is not permitted in this study.

This study is under review by a Data and Safety Monitoring Committee (DSMC). A DSMC is an independent group of doctors, scientists and ethicists. The DSMC can stop or change the study early if they determine that the study medications are not working, or that the study's goals have been met or cannot be met. If the study is stopped, your participation will end.

11) What will happen when the research study is over?

When the research study is over, you will stop taking the study pills. You will continue to receive care from your regular eye doctor during and after this study. You may be offered participation in another NIH study, if one is available.

12) Will your clinical and other test results be shared with you?

We will give you the results of all of your examinations. With your written request, we will send reports to your own doctors.

We will share with you in a timely manner any information we learn that may affect your willingness to continue to participate in the study.

13) Will the results of this research study be shared with you?

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

14) Will any of your blood, tissue, or other samples be stored and used for research in the future?

None of your blood will be stored or used for future research.

15) Will you receive any compensation (money or other) for taking part in this research study?

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.

You will not be paid to be in this study. We can assist you if you have problems related to transportation to the NIH.

16) Do any of the researchers or the NIH have a financial interest related to this research study?

None of the doctors in this study receives money or has a conflict-of-interest related to this research study.

17) What privacy and confidentiality procedures apply to the information gathered about you in this study?

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named or 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 other authorized persons.

18) What is the NIH's 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.

19) Who can answer your questions about the research and your rights as a research subject?

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, Catherine Cukras, MD, PhD; Building 10-CRC, Room 10C438, E-mail: cukrasc@nei.nih.gov. You may also call the NEI Clinic Coordinator Angela Kibiy, MPH, BSN, RN, at (301) 435-1833 or the Clinical Center Patient Representative at (301) 496-2626.

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 JANUARY 16, 2019 THROUGH FEBRUARY 14, 2020.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____