Macular Edema Ranibizumab v. Intravitreal anti-inflammatory Therapy (MERIT) Trial

Prototype Consent

20 Aug 2020

ClinicalTrials.gov identifier: NCT02623426

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JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH

INFORMED CONSENT DOCUMENT

Study Title: Macular Edema Ranibizumab v. Intravitreal anti-inflammatory Therapy (MERIT) Trial

Principal Investigator: Janet T. Holbrook, PhD, MPH

Sponsor: The National Eye Institute of the National Institutes of Health

PI Version Date: 20 August 2020

What you should know about this study

- You are being asked to join a research study.
- This consent form explains the research study and your part in the study.
- Please read it carefully and take as much time as you need.
- You are a volunteer. You can choose not to take part. If you join, you may quit at any time. There will be no penalty if you decide to quit the study.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to be in the study.

Purpose of research project

This research is being done to test treatments for persistent or recurrent macular edema in patients with the eye condition uveitis. Uveitis is inflammation inside of the eye. Macular edema is swelling of the retina at the back of the eye. Macular edema can cause vision loss.

The standard treatment for macular edema is injections of corticosteroid drugs into or near the eye. Sometimes the injections work only for a short time or the macular edema does not completely resolve. When this happens, the macular edema is said to be persistent and injections are needed more often. In other cases, the injections work well and the macular edema completely resolves but it reoccurs and needs to be treated with more injections. Repeated corticosteroid injections can cause side effects such as increase in eye pressure. This study will test whether other drugs that are not steroids are more effective that intravitreal corticosteroids in treating macular edema.

There are two types of corticosteroid drugs that are used as standard treatment for macular edema. One type is triamcinolone. Another type of corticosteroid drug that is used to treat uveitic macular edema is dexamethasone (also known as Ozurdex). Dexamethasone is in a pellet that releases medicine over time. Because the medicine is released over time, the treatment effect lasts longer. An applicator is used to inject a

dexamethasone pellet into the eye. It is a standard treatment for uveitic macular edema approved by the FDA.
Recent research has shown that other drugs injected into the eye can reduce macular edema in patients with uveitis. These drugs may have fewer side effects than the usual treatments. Two drugs that have been shown to reduce macular edema in small studies are methotrexate and ranibizumab (also known as Lucentis). Methotrexate is not approved by the FDA for treatment of any eye conditions. However, it has been used both systemically and by injection directly into the eye to treat some eye conditions. Ranibizumab is approved by the FDA for treating some kinds of macular edema but not macular edema related to uveitis.

This study will compare dexamethasone, methotrexate, and ranibizumab to find out which is the safest and most effective in treating persistent or recurrent macular edema. If you join the study, one of these drugs will be injected into the vitreous of your eye (intravitreal injection). The vitreous is the jelly like substance inside your eye. Intravitreal injection is used to place medicines inside the eye, near the retina. Placing the medicines inside the eye is done to avoid effects on the rest of the body.

Why you are being asked to participate
You are being asked to take part in this study because you have uveitis and macular edema that is persistent or recurrent. By persistent we mean that it does not respond completely or comes back sooner than expected after the standard treatment. By recurrent we mean that the macular edema responds completely but reoccurs. For people with persistent or recurrent macular edema, further treatment is often recommended and may be beneficial. However, which medications will provide the most effective and safest choices for further treatment remain unclear.

About 240 participants will be enrolled in this study at clinics in the United States, Australia, Canada, the United Kingdom, and India. Up to 48 participants will be enrolled at this clinic.

Sources of funding
This study is being conducted with funding from the National Eye Institute (NEI), a part of the National Institutes of Health (NIH). The NIH is a branch of the United States government. Genentech, a drug company, is donating one of the study drugs, ranibizumab (Lucentis) for participants in the U.S..

Procedures
<u>Screening phase:</u>
If you agree to take part in this study and sign this consent form, the study doctor will need to find out if you are eligible.

- You will be asked questions about your medical history, eye problems, and treatments you have received.

- Your vision will be tested.
- Your eye pressure will be measured.
- The front and back parts of your eye will be examined.
- You will have a test called optical coherence tomography (OCT) to measure the thickness of the central part of the retina to look for swelling.
- Women who are able to have children will have a pregnancy test. Women who are pregnant or breastfeeding may not join the study.

You also may be asked to sign a medical release of information form that will allow the study doctor to get copies of all of your medical records from other doctors or institutions.

Study phase

Study treatment

If you are eligible and agree to join this study, you will be randomly (by chance, like drawing a number out of a hat) assigned to one of the three study treatments:

- Dexamethasone pellet (Ozurdex) (0.7 mg)
- Methotrexate (400 micrograms in 0.1 mL)
- Ranibizumab (Lucentis) (0.5 mg in 0.05mL)

You will have an equal chance of receiving each treatment. Your study doctor will not get to choose which study treatment you receive.

You will have a procedure to inject the study treatment into one or both of your eyes, depending on which eye(s) needs treatment. Your study doctor or a doctor who works with your study doctor will perform the injection procedure. Usually the first injection(s) will be given right away (on the same day). The schedule for each study treatment is described below.

- Dexamethasone pellet (Ozurdex)
  - You will get an injection of dexamethasone at or soon following your first study visit.
  - If needed, you will get another injection of dexamethasone at your 8-week study visit
  - At your 12-week study visit or later
    - If needed, you may get another injection of dexamethasone.
    - If your macular edema does not improve, you may be treated according to your study doctor's best judgment.

- Methotrexate
  - You will get an injection of methotrexate at or soon following your first study visit.
  - If needed, you will get another injection of methotrexate at your 4-week study visit and/or your 8-week study visit.
  - At your 12-week study visit or later

  - If needed, you may get one or more additional injections of methotrexate spaced about 4 weeks apart.
  - If your macular edema does not improve, you may be treated according to your study doctor's best judgment.

- Ranibizumab (Lucentis)
  - You will get an injection of ranibizumab at or soon following your first study visit and at your 4-week and 8-week study visits.
  - At your 12-week study visit or later
    - If needed, you may get one or more additional injections of ranibizumab spaced about 4 weeks apart.
    - If your macular edema does not improve, you may be treated according to your study doctor's best judgment.

Before each injection, your intraocular (eye) pressure will be measured. You will receive numbing medicine around your eye to prevent you from feeling pain. Your eyes will be dilated using eye drops. The doctor will ask you to lie in a comfortable position and place numbing drops in your eye. Then your eye will be prepped and draped in the usual sterile fashion. Your eye and eyelids will be cleaned with an antiseptic solution. Your eye will be then held open. The drug will be drawn up in a sterile fashion in a syringe for injection. The tip of the needle will be inserted into your eye and advanced towards the center of the eye to inject the drug. You may feel slight pressure on the eye when this is done but you should not experience pain. Once your eyes are dilated, the procedure takes around 15 minutes. After the injection the doctor will check your eye. You will be monitored for any increase in eye pressure and allergic reactions.

If your study treatment does not seem to be working for you, your doctor may discuss changing your treatment. Your doctor may recommend other treatments according to his/her best medical judgment. This may mean switching to another treatment or adjusting the time between treatments. Even if your treatment changes, we want you to complete your study visits.

Study visit schedule
This is a 24-week (6-month) study. You will be asked to come in to the clinic for 7 study visits about a month apart. Your first study visit will last about 4 to 5 hours. The follow-up visits will last from 2 to 4 hours. You may need to visit the clinic more often for clinical care but that will not be part of the study.

Visit Number	Visit Type	Time after previous visit
1	Eligibility screening Study treatment assignment and administration	--------
2 (4-week study visit)	Follow-up	4 weeks after visit 1
3 (8-week study visit)	Follow-up	4 weeks after visit 2
4 (12-week study visit)	Follow-up	4 weeks after visit 3
5 (16-week study visit)	Follow-up	4 weeks after visit 4
6 (20-week study visit)	Follow-up	4 weeks after visit 5
7 (24-week study visit)	Follow-up	4 weeks after visit 6

Study procedures
The following procedures are part of regular care for your eye condition and will be done at every study visit.

- *Medical/ophthalmic history*: You will be asked questions about your health, eyes, and vision. This is to make sure that your study doctor knows about any side effects or other problems you may have.

- *Visual acuity*: You will be asked to read letters on a chart so your study doctor knows if your vision is getting better, worse, or staying the same.

- *External eye exam*: Your study doctor will look at the outside of your eye to check for any changes or abnormalities.

- *Slit-lamp exam*: Your study doctor will use a bright light to look at the inside of your eye to check for any changes or abnormalities.

- *Measurement of intraocular pressure*: A tool called a "tonometer" will be used to check the pressure inside of your eye. The tonometer applies a small amount of pressure on your cornea (clear part of the eye over the pupil).

- *Ophthalmoscopy*: Your study doctor will use a tool called an "ophthalmoscope" to look at the inside of your eyes to check for any changes or abnormalities. Your eyes will be dilated before this exam. Eye drops will be placed in your eyes to make the pupils larger. This will make it easier for the study doctor to see inside your eyes.

- *Optical coherence tomography (OCT)*: The test is like an ultrasound of your eye, except it uses light instead of sound waves. OCT measures the thickness of the back of the eye (central part of the retina) to look for swelling.

The following procedures also will be done during the study.

- *Questionnaires:* You will be asked to fill out questionnaires at every study visit. This is done for the study, not as part of regular care for your eye condition. The questions are about your health and vision and how they affect your life.

- *Gonioscopy:* This will be done at your first study visit only. It is part of regular care for your eye condition. Your study doctor will examine hidden structures in front of the iris (colored part of the eye) to check for any changes or abnormalities. A special lens called a "gonioscope" will be used.

- *Pregnancy test:* This is done for the study, not as part of regular care for your eye condition. If you are a woman who is able to become pregnant, you will have a pregnancy test at your first study visit. If you are assigned to methotrexate or ranibizumab as your study treatment, you will have pregnancy tests before each additional injection of study treatment. The test will be done on a urine sample. Some of the medicines and procedures in this study may not be safe for pregnant women.

We will monitor you throughout the study. During the study you should report all changes in your physical health or illnesses to the study staff. You will be also asked about medications taken at the same time as the study treatment.

Risks/discomforts

As with all research studies, some procedures may be uncomfortable or carry small risks. The treatments assigned during the study may also be uncomfortable and also have risks associated with them.

Study Treatments – possible side effects

***Dexamethasone pellet (Ozurdex)*:**

- Commonly reported events related to the drug
  - Elevated pressure inside your eye (IOP) which may require medicine to lower occurs at a rate of about 20% per eye year. IOP elevation, if it occurs, could last for several months. Your study doctor will monitor your IOP during the study. If it increases, your doctor will decide if you need medicine to lower it.

- Less frequently reported events related to the drug
  - Short-term visual disturbances (blurry vision or floaters)
  - Headache
  - Cataract development (clouding of the lens of the eye)
  - Elevated intraocular pressure (IOP) which may require surgery to control
  - In eyes that have had a procedure to open the posterior lens capsule, the medication pellet sometimes moves from the middle chamber to the front chamber of the eye
  - In patients with diabetes blood sugar may increase for a day or so after the injection

- Rare and serious events related to the drug
  - Perforation (hole) of the globe where there is thinning of the outer covering of the eye

- Possible side effects related to the intravitreal injection are provided later in this consent

Methotrexate:

- Commonly reported events related to the drug
  - Reversible corneal epitheliopathy (irritation on the surface of the cornea, the clear covering of the front of the eye). This condition usually resolves without treatment. If treatment is needed, usually lubricating eye drops are given.

- Rare and serious events related to the drug
  - Non-infectious endophthalmitis (severe inflammation of the tissues inside of the eye not related to an infection)

- Possible side effects related to the intravitreal injection are provided later in this consent

Ranibizumab (Lucentis):

- Commonly reported events related to the drug
  - Mild visual disturbances (blurry vision or floaters)
  - Temporary increase in eye pressure
  - Eye pain

- Rare and serious events related to the drug:

- Hypersensitivity reactions that may result in severe intraocular inflammation (swelling inside of the eye)
- There is about a 1 to 2 % risk of arterial thromboembolic events (for example, fatal or non-fatal stroke or heart attack). Intravitreal ranibizumab should be used with caution in patients with a history of stroke, heart attack, or transient ischemic attack (TIA).

Intravitreal injection:

All three study treatments will be given by injection directly into the vitreous of the eye (intravitreal injection). These are the risks related to intravitreal injections:

- Likely:
  - Gritty feeling in eye after injection
  - Sensation of a foreign object in the eye
  - Bleeding under the conjunctiva (subconjunctival hemorrhage)
  - Bleeding over the white of the eye which can be quite marked but will resolve in time
  - Seeing floaters; these will become smaller and disappear over a couple of weeks
  - Injecting any medication into the eye may result in increased pressure within the eye and inflammation

- Rare: Serious adverse reactions related to the injection procedure have occurred in less than 1 in 500 injections, including
  - Infection within the eye (endophthalmitis)
    - Symptoms are eye becomes red, sensitive to light, painful, or develops a change in vision or swelling around the eye
    - If any of these symptoms develop, call your study doctor right away.
    - An infection may lead to vision loss or in rare cases, loss of the eye.
    - Infections can be treated with a good result as long as you seek treatment quickly (preferably the same day).
  - Damage to the retina (retinal detachment or tear)
  - Eye inflammation
  - Bleeding within the eye (vitreous hemorrhage)
  - Iatrogenic traumatic cataracts

Study Procedures - risks associated with study procedures:

- *Visual Acuity:* You may feel frustrated if you are having difficulty reading some of the letters on the chart. You may experience some eye strain if you look at the chart for too long.

- *External eye exam:* You may find the bright light used during the exam to be uncomfortable, but it should not be painful.

- *Slit-lamp exam:* After the doctor dilates your eyes, your vision may be blurry and you may have trouble focusing on objects. You may be sensitive to bright light and you may need to wear dark glasses (or sunglasses). These side effects last only a short time.

- *Measurement of intraocular pressure (IOP):* You may experience a sensation of pressure when the measurement tool presses against your eye. You may find this sensation to be uncomfortable but not painful. Minor scratching of the corneal surface may rarely occur when the pressure in the eye is measured.

- *Ophthalmoscopy and OCT:* You may find the bright light used during these procedures to be uncomfortable, but it should not be painful.

- *Gonioscopy:* You may experience a slight burning from the eye drops your doctor uses during this exam. You may also experience blurred vision for several hours after the exam.

- *Pregnancy test:* You may have an emotional response to finding out you are pregnant if you were not previously aware.

- *Questionnaires:* You may get tired or bored when you are completing the questionnaires. You do not have to answer any questions that you do not want to answer.

For women

You may not join this study if you are pregnant or breastfeeding. If you are able to become pregnant, you must agree to practice birth control (abstinence, combination barrier and spermicide or hormonal) while you are in the study. This precaution is taken because the effects of study treatments on fetal development are not fully known. The effect of intravitreal ranibizumab and dexamethasone on fetal development are not known. Methotrexate is known to cause fetal death and/or birth defects when it is given systemically. Given systemically means when the drug is given by mouth or injection in a way that affects the whole body. The risk of harm to a fetus when methotrexate is injected into the eye at the dose used in this study is not known. The dose of methotrexate used in this study is lower than doses usually given systemically.
If you become pregnant while you are in the study, you must agree to let the study doctor know. You also will need to report any problems you have. We will ask you to let us know the outcome of your pregnancy even if you have finished the study.

General Risks

As with all research studies, it is possible that study procedures may involve unknown risks.

Your macular edema may not get better while you are in the study. It is possible that your macular edema might not respond to study treatment and could get worse. If this happens you will be treated according to your study doctor's best medical judgment. You will be told of any findings that might change your decision of whether to remain in this study.

If you have any questions or concerns regarding any of these risks, please consult with your study doctor. If you experience any illness or discomfort during the study, you should notify your study doctor.

Benefits

The benefits of taking part in this study for you are unknown because it is not clear which treatment will work best for which patients. You will receive a general assessment of your uveitis and your macular edema. Information from this study may be helpful in the future to other people with uveitis and macular edema. The information also may help you because you may need treatment for macular edema in the future.

Payment

You will receive $75 for each study visit. If you complete all 7 visits you will get a total of $525. If you leave the study before finishing all visits, you will be paid for the visits you have completed.

Protecting data confidentiality

All research projects carry some risk that information about you may become known to people outside of the study. In order to minimize this risk, your name and other identifying information will be kept private. Data collected from your study visits will be sent to the Coordinating Center. The Coordinating Center is located at The Johns Hopkins University in Baltimore, Maryland. Your information will be labeled with a unique number and special code to keep it private. The unique number and code cannot be linked to your name except at the clinical center where you complete visits. Some of the OCTs taken of your eyes will be sent to the Photograph Reading Center located at the University of Wisconsin in Madison, Wisconsin. These images will also only be identified by the unique number and special code

People at Johns Hopkins University, the National Eye Institute, the Food and Drug Administration, and the Institutional Review Board at this clinic may see the data collected from you during the study and review your records. Also people from Genentech, the company that donated one of the study drugs, may review your records related to this study. These people work on the study and/or need to make sure the study is being done correctly. They may see your identifying information as part of their review. However, they also must keep this information private.

Results from this study may be published in the medical journals but you will not be identified by name.

When you join this study, you give permission for the study doctor or staff to contact you in the future about participating in other research studies. You do not have to join any other studies unless you want to.

Certificate of Confidentiality
Your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.
It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Alternatives to procedures or treatments
You may choose not to take part in this study. If you do not participate, you can receive the standard treatments for macular edema outside of this study. You may receive treatments similar to the treatments in this study at the discretion of your doctor. You can discuss with your doctor which treatments will benefit you the most.

Cost of participation in the study
You and/or your insurance will be charged for the regular medical care you need, in the same manner as if you were not part of this study. Such care includes the cost of medications used to treat uveitis and macular edema other than your assigned study treatment. The study will provide your assigned study treatment as follows:

- If you are assigned to receive Ozurdex (dexamethasone pellet), the study will provide for up to 3 pellets as needed for each eligible eye;
- If you are assigned to receive methotrexate, the study will provide up to 7 injections as needed for each eligible eye.
- If you are assigned to receive ranibizumab (Lucentis), the study will provide up to 7 injections as needed for each eligible eye.

Genentech, the company that makes ranibizumab (Lucentis), is donating this drug for the U.S. study centers. The study will pay for the other two study treatments, and for the cost of ranibizumab (Lucentis) for participants at centers outside of the U.S..

If you receive a treatment that you were not randomly assigned to receive, the study will not provide that treatment. For example, if you are randomly assigned to receive methotrexate injections and the study doctor decides the injections are not helping, he/she may recommend you receive an Ozurdex pellet. The cost of that Ozurdex pellet will be billed to your insurance and you will be responsible for any co-pays.

You will also be responsible for costs not covered by insurance (for example, co-payments) for regular medical procedures and non-study medications just as you would be if you were not in the study.

What happens if you leave the study early?

You can agree to be in the study now and change your mind later. If you wish to stop participating in the study, please tell us right away. Leaving this study early will not stop you from getting regular medical care at [Johns Hopkins University].

If you leave the study early, [Johns Hopkins University] may use or give out your health information that it has already has if the information is needed for this study or any follow-up activities.

Your study doctor may take you out of this study if staying in the study would be harmful to you or if you fail to follow instructions. The sponsor or regulatory agencies may stop this study at any time without your consent. If this happens, you will be notified and your study doctor will discuss other options with you.

Conflict of Interest

A conflict of interest occurs when a researcher or the University has a financial or other interest that might affect the researcher's judgment when conducting a research study. In some situations, the results of a study might lead to a financial gain for the investigator(s) and/or [Johns Hopkins]. All such conflicts must be disclosed to the Conflict of Interest Committee. At this time, [Johns Hopkins University] is unaware of any potential conflicts of interest with regard to this research study.

Payment of treatment costs for injury or illness from study participation

If you are hurt or become ill as a result of being in this study, contact your study doctor immediately. Your study doctor will arrange for short-term emergency care or referral if it is needed. However, neither [Johns Hopkins University] nor the NIH have plans that will pay you if you are hurt or have other bad results. Costs of such treatment may be billed to you or your insurance. Your health insurance may not pay for treatment of injuries as a result of your participation in this study. You do not waive any of your legal rights or release anyone from liability for negligence by signing this document.

Clinical Trial Registration

A description of this clinical trial is 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.

Authorization for Disclosure of Protected Health Information for Research
We are asking you to authorize the disclosure and use of your private health information for this research study. By signing this authorization, you agree that we may release your private health information to us for use in this research study:

Your private health information that will be used for this research includes things learned by the procedures described in this consent form. The research team at your clinic also will collect your name, address, phone number, social security number, and other information that can identify you and link you to the health information collected in the study. Your date of birth will be included in the information sent to the Coordinating Center but other identifiers such as your name will not. After this study ends, the Coordinating Center will continue to store the data collected from you and other participants during the study. The Reading Center will continue to store the images of your OCT tests. The data and images may be used for future research in uveitis and other health topics.

The people who may receive or use your private health information include the researchers and their staff. The researchers and their staff are required by the Federal Privacy Rule to protect your private health information. By signing this Authorization, you permit them to release your information to the researchers for use in this research study. The researchers will try to make sure that everyone who needs to see your private information for this research keeps it confidential, but we cannot guarantee this. Although the researchers may not be covered by the Federal Privacy Rule, they will make an effort to protect your information using the same standards.

Some other people may see your private health information outside of the research team. They may include the Coordinating Center, sponsor of the study, study safety monitors, government regulators, and legal compliance staff. All these people must also keep your information confidential.

You do not have to sign this Authorization, but otherwise you may not join the study. It is your choice.

Your Authorization does not have an expiration date; it will continue as long as the research continues. You may change your mind and take back this Authorization at any time. If you take it back, the researchers may still use the private health information they have collected about you to that point. To take back the Authorization, you must contact the researcher.

Who do I call if I have questions or problems?

- Call the principal investigator, [Janet Holbrook at 410-955-0930] if you have questions, complaints, or get sick or injured as a result of being in this study.

- Call or contact the [Johns Hopkins Bloomberg School of Public Health IRB Office] if you have questions about your rights as a study participant. Contact the IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:

  Address: [Johns Hopkins Bloomberg School of Public Health
  615 N. Wolfe Street, Suite E1100
  Baltimore, MD 21205]
  Telephone: [410-955-3193]
  Toll Free: [1-888-262-3242]
  Fax: [410-502-0584]
  E-mail: [irboffice@jhsph.edu]

What does your signature on this consent form mean?
Your signature (or thumbprint/mark) on this form means:

- You have been informed about this study's purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions before you sign.
- You have voluntarily agreed to be in this study.

_____ _____ _____
Print name of Adult Participant Signature of Adult Participant Date

_____ _____ _____
Print name of Legally Authorized Representative (LAR) Signature of LAR Date

_____
Relationship of LAR to Participant

Ask the participant to mark a "left thumb impression" in this box if the participant (or participant's parent) is unable to provide a signature above.

_____ _____ _____
Print name of Person Obtaining Consent Signature of Person Obtaining Consent Date

Give one copy to the participant and keep one copy in study records