The University of New Mexico Health Sciences Center
Consent to Participate in Research
3/27/2015

Study title: Impact of Ranolazine on Coronary Microcirculatory Resistance- A prospective single center study to evaluate the effect of Ranolazine on microcirculatory resistance.

Introduction
You are being asked to participate in a research study that is being done by Bina Ahmed, MD, who is the Principal Investigator and associates from the Department of Internal Medicine, Cardiology. This research is studying the effect of the drug Ranolazine (Ranexa) on patients with chest pain due to abnormal function of small heart arteries (microvessels) without blockages in the main heart arteries. Participants enrolled in this study will have already had a heart catheterization prior to enrollment. Participants will undergo a follow up heart catheterization four weeks after enrollment. This is not done as standard of care but is part of the research study to re-assess small vessel function after the four week treatment with Ranexa. Although the idea for this study is solely Dr. Ahmed's, the study is being 'sponsored' by the company which makes Ranexa (Gilead Pharmaceuticals).

Background
The heart has small blood vessels which are essential and play a complex role in regulating blood flow to the heart muscle. Patients who have abnormal function of the small heart arteries without having blockages in the main arteries have chest pain which brings them to the hospital recurrently. These patients are at risk for dying from heart related issues later in life compared to patients who don't have this dysfunction.

To date, there are limited therapies known to treat small vessel dysfunction. Ranexa is a medication that has been shown to improve symptoms of chest pain in these patients but whether this is actually related to improving small vessel dysfunction remains unknown. Our study is looking to see what happens to abnormal small vessel function after treatment with Ranexa.

You are being asked to participate in this study because you have been told you have small vessel dysfunction in your heart arteries without having blockages in your main heart arteries. We are going to ask 20 people to take part in this study at the University of New Mexico.

This form will explain the research study, and will also explain the possible risks as well as the possible benefits to you. We encourage you to talk with your family and friends before you decide to take part in this research study. If you have any questions, please ask one of the study investigators.

What will happen if I decide to participate?
If you agree to participate, the following things will happen:

<u>Enrollment visit</u>

Once you are diagnosed with small vessel dysfunction in your heart arteries and are willing to participate, you will be enrolled into the study. You will have to do the following during the enrollment visit:

1: Pregnancy testing: If you are a female with the possibility of being pregnant, your urine will be tested to see if you are pregnant. You will not be eligible to participate if you are pregnant,
2: Questionnaires: You will be asked to fill out a questionnaire that evaluates your activity level and the quality and quantity of your chest pain episodes.
3: ECG (electrocardiogram): We will perform an ECG if not already done. An ECG takes recordings of the electrical activity of your heart from small, sticky patches called electrodes attached to the chest, arms and legs. This test does not carry any risks to you and is done routinely.
4: History: We will ask your permission to obtain your past medical history including demographic, medication and social history.
5: Treatment with Ranexa: You will be started on the study medication, Ranexa. This is a drug that is approved to treat chest pain symptoms. You will take the drug twice a day for a total of 4 weeks. The first week you will take 500 mg tablets twice a day followed by 1000 mg tablets twice a day for 3 additional weeks.

It is very important that you take the study medication as instructed throughout the study. Do not miss any tablets. If at any time you experience any problems or decide you no longer wish to continue to take study medication you should not stop taking the study medication without first contacting the study nurse or the study doctor.

Your study doctor will discuss with you medications that you may or may not take during the study because there are certain medicines that you should not take in addition to the trial medication. It is very important that at each visit you tell your study doctor about all medications that you are presently taking. This includes prescriptions drugs, over-the-counter medicines and vitamins. It is very important that you take the study drug given to you just as the doctor tells you to.

You will also not be able to start any new medications or change any of your old medications during the 4 week study period. If you must start a new medication while in the study, please tell the study staff before taking it. They will decide if it conflicts with the study drug. You may be removed from the study if the study doctor feels it would be in your best interest. It is essential that all medication related questions be discussed with the study team prior to starting, stopping or changing any doses.

Please inform your study doctor if you receive additional medicine from another doctor for the treatment of any diseases at any time during your participation in the study. Please tell your study doctor or study staff if you have any unusual symptoms at any time during the study.

It is very important that you return all unused study medication at every study visit. The study medication must be taken only by the person for whom it has been prescribed and it must be kept out of the reach of children or persons with limited capacity to read or understand.

Phone Follow-up:

At the end of the first week after you have started Ranexa, a member of our study team will contact you by phone. You will be asked about any side-effects that you are experiencing. At this time if you are tolerating the medication, you will be asked to increase the dose to 1000 mg twice a day for the three additional weeks. You will then be contacted every week for two additional weeks to ensure that you are doing well on the therapy.

Follow-Up Visit:

At the end of four weeks of treatment with Ranexa, you will be scheduled to return to undergo another heart catheterization to re-assess small vessel function. This test will be a shorter version of the heart catheterization you had four weeks prior to the study. We will use the wrist or leg artery to get access into the arterial system. This is done after application of sufficient local anesthetic and insertion of a hollow tube similar to an IV line. First we will pass a catheter into the pumping chamber of the heart and measure pressures inside.

We will then use a different catheter to engage your heart artery (most likely the left main artery) and inject dye to see what the artery looks like using XRAY. We will then place a very small wire in your heart artery and measure the function of your small heart arteries. During this test, we give you a medication called adenosine which may make you feel flushed transiently while we assess the effect of Ranexa on the small vessels via the small wire in your heart arteries.

Once we are done, we will remove our equipment. You will be monitored afterwards for 3-5 hours prior to being discharge home. You will be given further instruction about care of the access site either in your wrist or leg. You will be asked to not lift anything greater than 10lbs for about 5 days as your access artery heals.

During the follow-up visit, we will ask you to fill out the two questionnaires that you filled out at the screening visit regarding your activity level and the quality and quantity of your chest pain episodes.

How long will I be in this study?

Once you agree to enroll, you will be in the study for a total of four weeks. The study involves 1 additional visit over a period of 4 weeks and a phone follow-up at 1,2 and 3 weeks. The visit for the f/u heart catheterization will require you to be in the hospital for possibly 8-12 hours. After the procedure, you will be advised not to lift anything heavier than 10 pounds for 5 days and if your leg artery was used, to not engage in prolonged climbing for 5-7 days.

What are the risks or side effects of being in this study?

There are several possible risks and side effects you may experience from participating in this clinical study.

1: Risks and side effects of Ranexa
Minor side effects (5-10 out of a 100 people):

- feeling like you might pass out;
- swelling in your hands, ankles, or feet;
- slow, fast, or pounding heartbeats;
- tremors or shaking;
- blood in your urine;
- urinating less than usual or not at all;
- shortness of breath;
- constipation

Serious side effects (less than 1 out of a100 people):

- Prolonged QT interval: You may develop a long electrical interval (called prolonged QT interval) and a dangerous fast heartbeat. This happens in less than 1% of people. We will check your QT interval on an ECG which will be done at the time of enrollment to make sure you are not at risk for this.
- Liver failure: Ranexa does not cause liver failure but patients with liver failure should not be on Ranexa as they will not be able to metabolize the drug.
- Ranexa should not be taken with certain medications that may alter its metabolism. The study team will carefully review all your medications to make sure there are no concerning interactions. In addition, you should not begin any medications for the duration of study without discussing it with the study team.

2: Risks of Study procedures

Risks of heart catheterization:

a. Bruising around catheter in your artery (approximately 1-2 out of 100 patients)
b. Major Bleeding which may require blood transfusion (less than 1 out of 400 patients)
c. Serious reaction or rash to contrast dye (less than 2 out of 1000 patients)
d. Contrast dye induced kidney failure (less than 2 out of a 100 patients)
e. spasm of your access artery (2-4 out of 400 patients)
f. Access artery perforation (0.5-1 out of 100 patients)
g. Local nerve damage (less than2 out of 1000 patients)
h. Infection (less than1 out of 400 patients)
i. Stroke, heart attack or death (less than2 out of 1000 patients)

Risk of small vessel testing:

Bleeding: We will give you medicines which thin your blood during the procedure. These are given for heart catheterization. On average, risk of having a major bleeding problem which requires blood transfusion is less than 1 in 400 patients. We monitor the extent of how thin your blood is very carefully during the procedure.

Risks of placing a small wire in your heart arteries: Because we will be placing a small wire into your heart artery, there is a very small risk of causing trauma and a tear in the artery. On average, the risk of causing a tear or spasm of your artery is less than 2 in a 1000. If spasm does develop, will treat this with giving nitroglycerin down your heart arteries to release the spasm. Death resulting from tearing of the heart artery is extremely rare but possible (less than 2 in 1000 patients).

Risk of Adenosine infusion:

We will administer Adenosine through your IV line in your arm while we perform small vessel function testing. The drug will be administered for about 5 minutes. Adenosine is the same medication given to patients who undergo a chemical stress test. We will use the same weight based dose. Adenosine can cause temporary slowing of your heart rate (less than1 in 100 patients), give you

temporary chest pain (1 out of 5 patients), flushing (15 out of 100 patients), shortness of breath (5-10 out of 100 patients). Because the medication is in your system for seconds, the effects do not last long.

Other potential risks:

There is the possible risk of physical stress, emotional distress, inconvenience and possible loss of privacy and confidentiality associated with participating in a research study.

Follow-up cardiac catheterization will be associated with additional radiation exposure. This will be less than that received during the initial heart catheterization. Efforts will be made to limit total exposure and we anticipate 2-5 minutes of additional xray exposure will be used. There will be exposure to different organs but centered around your chest and abdominal areas. This may amount to a years worth of natural background radiation that an average person receives.

Risk of placing an IV line: Risk associated with this are minimal but include site infection and bleeding. Both of these are extremely rare and careful septic precautions are strictly adhered to.

For more information about risks and side effects, ask the investigator.

What are the benefits to being in this study?

There may or may not be direct benefit to you from participating in this study. But if you have been diagnosed with small vessel dysfunction, the findings of this study may help you if the study drug is shown to improve this function. Similarly, if the drug is shown not to improve small vessel function specifically for you, than the drug can stopped and other treatments pursued. This is the purpose of the study is to show that there is actual improvement in function on treatment with Ranolazine. It is hoped that information gained from this study will help in the treatment of future patients with small vessel dysfunction. Receiving a second cardiac catheterization is not routinely done to assess response to drug. It is only being done because of this study protocol. The follow-up cardiac catheterization along with all associated risks is purely for research to understand the effects of Ranexa on small vessel dysfunction.

What other choices do I have if I do not want to be in this study?

You do not have to participate in this study to receive treatment for your condition. You can receive this drug without participating in this study. Also, there are other medicines available for the treatment of small vessel dysfunction . Participation in this study is not a substitute for your usual ongoing medical care by your regular doctor or specialist. The study doctor will tell you more about the risks and benefits of participating in this study as compared to the risks and benefits of alternative treatments.

How will my information be kept confidential?

We will take measures to protect your privacy and the security of all your personal information, but we cannot guarantee confidentiality of all study data.
Information contained in your study records is used by study staff, and it will be shared with the sponsor of the study, Gilead Pharmaceuticals. The University of New Mexico Health Sciences Center Human Research Review Committee (HRRC) that oversees human subject research, and the Food and

Drug Administration and/or other entities that may have access will be permitted to access your records.

There may be times when we are required by law to share your information. However, your name will not be used in any published reports about this study. A copy of this consent form will be kept in your medical record.

Information (without your name) will be entered into a computer database/locked file cabinet in the research nurse's office. Data will be stored for 1-2 years, and then will be destroyed.

Medical information created by this study will become part of your hospital medical record since it will be used to treat you.

What are the costs of taking part in this study?

You (and/or your insurance company) will not be responsible for the costs of the follow-up heart catheterization or the cost of Ranexa taken during the four weeks. However if you agree to participate there may be cost of personal time necessary to attend study visits, time missed from work, parking or other transportation fees. If the drug is found to be making improvements to your condition, we will recommend it be continued. But the drug sponsor will not cover the cost of the drug after the study is completed in four weeks. At this time, if we decided to continue your treatment, the cost will have to be covered by you or your insurance company.

You will still be responsible for the cost of your usual ongoing medical care, including procedures and/or non-study medications that your study doctor or regular doctor requires during this study as part of your usual medical care.

What will happen if I am injured or become sick because I took part in this study?

If you require medical care as a result of a complication specifically resulting from the study procedure or study drug, UNMHSC will provide you with emergency treatment. This will be billed to your insurance company. No commitment is made by the University of New Mexico Health Sciences Center (UNMHSC) to provide free medical care or money for injuries to participants in this study. Reimbursement for all related costs of care will be sought from your insurer, managed care plan, or other benefits program. If you do not have insurance, you may be responsible for these costs. You will also be responsible for any associated co-payments or deductibles required by your insurance. It is important for you to tell your study doctor immediately if you have been injured or become sick because of taking part in this study. If you have any questions about these issues, or believe that you have been treated carelessly in the study, please contact the Human Research Review Committee (HRRC) at the University of New Mexico Health Sciences Center, Albuquerque, New Mexico 87131, (505) 272-1129 for more information.

Will I be paid for taking part in this study?

You will be not be paid to participate in this study

How will I know if you learn something new that may change my mind about participating?

You will be informed in a timely manner of any significant new information pertaining to your safety that may influence your willingness to continue participation in the study. If new scientific information is obtained about any of the study medications during the course of the study, your study doctor or study staff will provide this information to you. This will be done so you can decide whether or not you wish to continue to participate in the study.

Can I stop being in the study once I begin?

Your participation in this study is completely voluntary. You have the right to choose not to participate or to withdraw your participation at any point in this study without affecting your future health care or other services to which you are entitled.

The study doctor may remove you from this study if:

- Staying in the study would be harmful.
- You need treatment not allowed in this study.
- You fail to follow instructions.
- You become pregnant.
- The study is cancelled.

In addition, you may be taken out of the study if for any reason your doctor feels it would be in your best interest for you to stop participating. If you should decide to leave the study you should tell the study doctor or study staff. They will make sure that proper procedures are followed and a final visit is made for your safety. If you leave the study early, you must return all unused study medication. You may be asked questions about your experience while you were in the study. You may be asked to have follow-up evaluations such as laboratory tests or a physical examination to help your withdrawal from the study happen safely.

Whom can I call with questions or complaints about this study?

If you have any questions, concerns or complaints at any time about the research study, Bina Ahmed, MD or her associates will be glad to answer them at 505-272-9223, Monday through Friday from 8:30 AM to 5:00 PM. If you need to contact someone after business hours or on weekends, please call 505-272-1720 and ask for the cardiology interventionalist on call. If you would like to speak with someone other than the research team, you may call the UNMHSC HRRC at (505) 272-1129.

Whom can I call with questions about my rights as a research subject?

If you have questions regarding your rights as a research subject, you may call the UNMHSC HRRC at (505) 272-1129. The HRRC is a group of people from UNM and the community who provide independent oversight of safety and ethical issues related to research involving human subjects. For more information, you may also access the HRRC website at http://hsc.unm.edu/som/research/hrrc/.

CONSENT
You are making a decision whether to in this study. Your signature below indicates that you have read the information provided (or the information was read to you). By signing this consent form, you are not waiving any of your legal rights as a research subject.

I have had an opportunity to ask questions and all questions have been answered to my satisfaction. By signing this consent form, I agree to participate in this study. A copy of this consent form will be provided to you.

_____	_____	_____
Name of Adult Subject (print)	Signature of Adult Subject	Date

INVESTIGATOR SIGNATURE
I have explained the research to the subject or his/her legal representative and answered all of his/her questions. I believe that he/she understands the information described in this consent form and freely consents to participate.

_____
Name of Investigator/ Research Team Member (type or print)

_____	_____
(Signature of Investigator/ Research Team Member)	Date