

SECTION 2

NON-TECHNICAL ABSTRACT

PURPOSE AND BACKGROUND

The *Principal Investigator* is participating in a multi-center research trial sponsored by Berlex Laboratories Inc. to determine if a gene that stimulates the growth of new blood vessels in the heart can benefit patients with angina pectoris. Angina pectoris is caused by narrowing of the blood vessels to the heart. Selected patients have been asked to participate in this trial because they have angina pectoris. The vascular growth treatment called Ad5-FGF4 is an experimental treatment. It has been designed to provide gene therapy with the FGF4 gene to cause new blood vessel growth and relieve angina pectoris. Gene therapy refers to a new form of therapy in which genes are introduced into cells and the cells then produce the specific protein that the gene directs, in this case a protein known as fibroblast growth factor 4 (FGF4).

The gene is carried into the heart cells by a modified virus. The modified virus has been constructed from adenovirus (Ad5), a virus which sometimes causes the common cold. The virus has been modified in a way so that it cannot multiply and thus cannot cause infection. The FGF4 gene has been added to the modified adenovirus. The FGF4 gene is being used because FGF4 has been found to stimulate the growth of new blood vessels. In an experimental animal model in pigs that mimics human disease it was found that therapy with Ad5-FGF4 resulted in production of FGF4 and improved blood flow to the heart to relieve an experimentally induced condition equivalent to angina pectoris.

Patients are being asked to participate in this study because during times of stress, their heart has insufficient blood flow resulting in angina pectoris. Patients' active participation in this study will last about four months.

If you agree to participate in the study, the following events will occur:

1. Each patient will perform two or three exercise tolerance tests on a standard treadmill to test if the patient can exercise for at least three minutes, whether the EKG taken during the treadmill test confirms that the patient has angina pectoris, and whether there is less than 25% variability in exercise performance.
2. Blood tests, a urine sample, a physical examination, a mammogram (female subjects only) and a chest x-ray will be performed. Each patient will have an eye exam before and after treatment by an ophthalmologist to confirm the absence of gene therapy effect in the eye. The patient will have a stress echocardiogram which involves viewing the heart with sound waves. In order to induce stress a medication called dobutamine, similar to adrenaline, will be infused into a vein in the patient's arm to increase the heart rate. Infusion of this drug has a slight risk of causing irregularity of heart rhythm which might require treatment (less than 1 in 1,000 patients).

3. Patients will undergo cardiac catheterization and coronary angiography. If the narrowing in the coronary arteries is such that therapy with AD5 FGF4 is appropriate (about 70% chance) and as the patient fulfills inclusion criteria after tests listed in (1) and (2), he or she will proceed with the study. If not, the patient's doctor may recommend other types of treatment.
4. Ad5-FGF4 or placebo will be injected by catheter into the coronary artery supplying blood to the heart. Each patient will have a three in four chance of receiving the active product, and a one in four chance of receiving placebo. The patient will be observed in the hospital for up to several days.
5. Seven days after treatment the patient will return to the hospital to be examined and have blood and urine tests. A small sample of blood will be drawn from the vein in his or her arm and a urine sample collected.
6. Fourteen days after treatment the patient will again return to the hospital for blood tests, urine tests, and a chest x-ray.
7. Four weeks after treatment the patient will return to the hospital for repeat blood tests, urine tests, treadmill exercise test and stress echocardiogram.
8. Eight weeks after treatment each patient will return to the hospital to be examined and have blood and urine tests.
9. Twelve weeks after treatment the patient will return to the hospital for a repeat exercise test, a stress echocardiogram, physical examination, blood and urine tests and an eye exam.
10. Six months and one year after treatment the patient will be called for follow-up and asked some follow-up questions regarding his or her general health and symptoms of angina pectoris.

Because gene therapy is new and long term effects are not known, there is a need for careful evaluation. It is very important that each patient return for all visits and answer questions at six months and one year after treatment. We are requesting that the study participants notify his or her doctor regarding a change of address.

This study may involve the following risks or discomforts:

Risks associated with using an adenovirus for gene therapy in the human heart are unknown. Potential risks include:

1. The adenovirus being used is modified so that it cannot multiply and cause infection. However, it is remotely possible that during the study the virus will acquire the ability to cause infection, although this is unlikely. It is known that the adenovirus from which this modified adenovirus was derived is typically associated with the common cold. Therefore, serious complications are unlikely.
2. A patient could have a mild allergic reaction. It is also possible, although unlikely, that a patient's immune system reacting to the virus could cause inflammation to the heart. While animal studies fail to show any evidence of heart inflammation, this study will be the first time that Ad5-FGF4 is used in patients.

3. Potential risks to a fetus are unknown, so women of child bearing potential are not being enrolled in this trial. If a woman and could become pregnant, she will not be enrolled in this trial. When a male enrolls, he must agree to abstain from intercourse or use a condom for 12 weeks following treatment.
4. Ad5-FGF4 causes the production of a growth factor, FGF4. While animal studies indicated that the production of the growth factor was confined to the heart, it is possible that the growth factor could circulate in the blood and have affects at distant sites. Therefore, growth of blood vessels at sites outside the heart could occur. For example, if this growth is on the skin, it could result in the formation of small capillaries (hemangiomas). In the eye, abnormal blood vessel growth could interfere with vision. Vision and evidence for these vascular growths in the eye will be checked by an ophthalmologist. While we do not expect this vascular growth to occur any place other than the heart based on animal experiments, this is the first time that Ad5-FGF4 is being used in patients.
5. Some patients will receive placebo. The patient and his or her doctor will not know whether the patient is receiving Ad5-FGF4 or placebo. This study will involve increasing doses of Ad5-FGF4. The lowest doses will be used in the first patients and progressively increased for subsequent patients if no serious side effects are observed. Since patients will only receive one dose, some patients will receive low doses. Some patients will receive higher doses. While animal studies indicated that the beneficial effects occurred at doses which did not have any toxic reaction, there is no absolute assurance that the same will be true in patients.
6. Animal studies have not shown any evidence that adenovirus gene therapy can alter the DNA in your reproductive cells and not shown any evidence of cancer production. While such side effects are therefore very unlikely, they could occur.
7. While the growth factor FGF4 does not cause cancer, it could stimulate the growth of already existent malignant tumors. While each patient's doctor has examined and performed tests to detect tumors, it is possible that an occult tumor could be stimulated to grow faster by FGF4.
8. We expect that most treatment effects will occur within 4 weeks.

RISKS ASSOCIATED WITH OTHER PROCEDURES THAT ARE PART OF THIS STUDY

- 1 . Treadmill exercise testing carries a slight risk of causing heart rhythm abnormalities, occurring in less than 1 in 10,000 patients. Should such arrhythmias occur, proper drugs and equipment are readily available for treatment.
- 2 . The stress echocardiogram test is associated with some slight risks. Infusion of dobutamine to make the heart beat faster could cause irregularity of the heart rhythm. The risk of such arrhythmias is probably less than 1 per 1,000 patients. Should these arrhythmias occur, treatment is readily available. Occasionally, dobutamine may cause nausea, shortness of breath or headache..

3. Risks associated with cardiac catheterization: The cardiac catheterization procedure involves insertion of a catheter in both an artery and a vein, passage of those catheters into the heart, injection of contrast material for x-ray, injection of the test product into the artery supplying the heart at the treatment phase, withdrawal of the cardiac catheters and continued hospitalization and observation over night. Patients will be asked to sign separate consent forms for cardiac catheterization at the time of the cardiac catheterization. In general, risks associated with the catheterization procedure include damage to the artery or vein which might require surgical repair, heart rhythm abnormality which might require treatment in the catheterization laboratory, damage to the arteries within the heart which might require emergency cardiac surgery and/or other complications including death. While these complications are relatively rare, they could occur. The risk of death from cardiac catheterization is less than 1 per 1,000 patients.

ADDITIONAL RISKS

This study involves the investigational agent Ad5-FGF4 which has never been given to patients prior to the current study. While animal tests suggest that this will be safe and effective, and no evidence of serious toxicity was found at the doses being used, it is possible that additional risks and/or discomforts which are presently unknown and unforeseen could occur.

BENEFITS

It is not known at the present time if Ad5-FGF4 will relieve angina pectoris. The benefit received from this experimental treatment may be none, minimal, or significant. Each patient will have a one in four chance of receiving placebo.

ALTERNATIVES

At the present time, patients have other treatment options for your angina pectoris:

1. The patient may continue on medical therapy.
2. Depending on the extent and location of narrowing in the coronary arteries, a patient could undergo coronary angioplasty. The patient's doctor can discuss this possibility with each patient. Coronary angioplasty is effective in relieving angina pectoris.
3. Depending on the location and severity of the narrowing in the coronary arteries, the patient could undergo coronary artery bypass graft surgery to relieve angina pectoris. The patient's doctor can discuss this possibility with each patient. Coronary bypass surgery is effective in relieving angina pectoris.