INSTITUTE: National Institute of Allergy and Infectious Diseases

STUDY NUMBER: 11-I-0057 PRINCIPAL INVESTIGATORS: Frank Maldarelli, M.D.

STUDY TITLE: Effect of Interferon Alpha 2b Intensification on HIV-1 Residual Viremia in Individuals Suppressed on Antiretroviral Therapy

Continuing Review Approved by the IRB on 06/15/15
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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.

Purpose of this Study
You are invited to participate in this study because you have HIV infection and the amount of HIV virus in your blood is suppressed below the limit of detection on antiretroviral therapy (ARVs). The therapy you are taking for HIV is effective in controlling but not curing the HIV infection. Low levels of HIV are present even when the amount of HIV virus in your blood is measured below the limit of detection for virus (<50 copies RNA/mL plasma). The source of the small amount of HIV is unknown. It may come from a low-level infection, where new cells are continually infected with HIV. It is also possible that the virus is coming from cells that live for a long time after infection. We would like to learn more about the origin of residual HIV, because it will help us to understand the virus infection. We are interested in finding out whether antiviral agents other than the ARVs can affect the level of residual HIV in the blood. In this study we are investigating whether interferon alpha/Pegintron/Pegylated interferon alpha 2b will affect the level of HIV virus in the blood of individuals whose virus is suppressed on antiretroviral therapy. Interferon is a natural substance made by the

body to combat viral infections. Interferon can also be made as an injectable drug, called pegylated interferon alpha 2b (PEGINTRON®), which has been approved by the FDA for use in hepatitis C infection. In several earlier studies of HIV infected individuals who were not on any antiretroviral therapy, PEGINTRON® was shown to reduce the level of HIV in the blood. We are doing the present study to learn whether PEGINTRON® therapy will also reduce the residual low levels of HIV in patients who are already taking antiretroviral therapy. In this study, participants will receive weekly PEGINTRON injections for 4 weeks using the standard dose of PEGINTRON that is approved by the FDA for hepatitis C infection. During the study, we will measure the levels of HIV in the blood using sensitive tests that can detect as little as 1 copy of HIV RNA in 3 milliliters of blood (about 6/10 of a teaspoon). After the 4 weeks of PEGINTRON®, we will obtain additional blood samples for a total of 1 year. We plan to study 10 individuals.

Eligibility to Take Part in this for Study

In order for us to determine whether it would be appropriate for you to participate in this study, we performed an initial evaluation to better understand the status of your HIV. This consisted of

- A visit to our clinic
- A history and physical examination
- Routine laboratory studies; pregnancy test if you are a woman of child-bearing potential
- Blood to measure the amount of HIV virus present using standard testing and ultralow viral load test
- Blood specimens for storage
- Participants who are considering getting a vaccine, including the seasonal influenza (flu) shot, should notify the study team.

Women of childbearing age will have a pregnancy test within 2 weeks prior to and another one on the day of the first dose of interferon. You should not get pregnant while participating in this study and should practice 2 different methods of contraception during this time. If you are pregnant, you cannot be in the study because we do not know how the study will affect the unborn fetus. If you are not pregnant, you will be asked to use 2 methods of birth control during the study.

Study Procedures

If the results of your evaluation indicate that you are eligible for PEGINTRON therapy and you decide to participate, you will return to enroll in the protocol. On the day you enroll, we will do another test to determine the amount of HIV virus in your blood, you will have two apheresis, and receive an eye examination. Apheresis is a procedure in which we obtain white blood cells. During apheresis, blood is removed through a needle in the vein of one arm, spun in a machine which permits separation of the desired blood component (usually white blood cells and plasma), and then the remainder is re-infused either through the same needle or through a needle in a vein in the other arm. An anticoagulant (a medication to prevent blood from clotting) is usually added to the blood while in the machine to prevent it from clotting during this processing. You will then come back to the clinic to begin a schedule of 4 weekly PEGINTRON injections (Days 0, 7, 14, and 21). The PEGINTRON injections will be given subcutaneously (small injection under the skin similar to an insulin shot).At each of these visits, you will see your case manager to review how you are feeling, and you will have blood taken for safety laboratory studies. If all remains well, you will receive your next injection of PEGINTRON®. If there are any abnormalities noted in the examinations, then we may delay the PEGINTRON injections. One side effect of PEGINTRON is to cause decreases in germ fighting white blood cells. If we find concerning decreases in white blood cell numbers, we will not give you PEGINTRON on your visit, but we will give you a medication called Filgrastim/GCSF/Neupogen to increase the white blood cell count. We will also schedule an additional visit to check that the Filgrastim is working.

Following completion of PEGINTRON therapy, you will return for additional blood tests on Days 28, 35, 42, 49, 56, 84, and Weeks 16, 24, 36, and 48; there is some flexibility about the exact days of sampling. Following the last visit at Week

48, your participation will be over. Antiretroviral medications will be provided by the protocol during this study. We plan to study a total of 10 patients for this study.

Benefits
There is no direct benefit to participation in this study. You will receive information about your health from the screening tests and physical examination. In the future, your participation may help us learn more about the causes, treatment, or prevention of HIV disease, immune dysfunction, and/or related diseases. The information we obtain may help us to improve our understanding of HIV infection. The viral load test we are using in this study has not been as extensively studied compared to commercial viral load tests, and the information we obtain will not be used in making any clinical decisions regarding your care.

Risks
The risks from this study are from blood drawing and apheresis from the PEGINTRON therapy, from the combination of PEGINTRON with antiretrovirals and other therapy you may be taking, and the risk of medications such as Filgrastim, which may be given during the study. Blood drawing is generally very well tolerated. Occasionally, pain from needle stick, bruising, or bleeding may take place; rarely fainting or infection may occur. The amount of blood drawn will be within the limits allowed for adult subjects by the NIH Clinical Center (Medical Administrative Policy 95-9: Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center). Like standard blood drawing from veins in your arm, apheresis is occasionally associated with local bleeding and bruising at the site of needle insertion. Lightheadedness can also occur, and people faint on rare occasions.

Risks of Interferon Alpha 2b (PEGINTRON®)
PEGINTRON® is a synthetic form of interferon alpha 2b, a natural substance made by the body in response to infections. PEGINTRON® has been approved by the FDA for use in individuals, including those with HIV, and to treat infection of the liver with the hepatitis C virus. PEGINTRON® has not been approved by the FDA to treat HIV alone. In this study, we will be using the standard dose of PEGINTRON® approved by the FDA for treating hepatitis C including individuals with HIV infection. There are a number of side effects that you may experience from the PEGINTRON® injections. In many patients, PEGINTRON may cause feelings similar to the flu, including fatigue (>50% of participants), fever (22%), muscle aches (54%), headache (56%), insomnia (23%). Gastrointestinal effects such as abdominal discomfort (15%), decreased appetite (22%), diarrhea (18%), indigestion (6%), nausea (26%), vomiting (7%), and dry mouth (6%) have been reported. Joint pain (23%) and dizziness (12%) have been reported. PEGINTRON® may cause changes in your mood. Depressive feelings occur in about one-third of individuals receiving PEGINTRON®; rarely, depressive symptoms have included suicidal thoughts and extremely rarely suicide has been reported. Our study will use PEGINTRON® for a short period (4 injections during 3 weeks) and we will monitor you very closely during the study for these changes in your mood. Infrequently, aggressive behavior, agitation, nervousness, or anxiety has been reported. There are also rare occurrences of autoimmune disorders, infections, eye, and vascular disorders associated with PEGINTRON® use. PEGINTRON has been reported to cause a problem with the retina in the eye, which is usually transient and completely resolves with continued treatment; all participants on this study will have eye examinations to monitor for this side effect. Other side effects associated with subcutaneous injection include pain and inflammation at the site of injection, cough (8%), shortness of breath (4%), or inflammation of the throat or sinuses (5-13 %). Other side effects have occurred infrequently as well.

PEGINTRON® may cause decreases in neutrophils, a kind of germ-fighting white blood cell. We will be monitoring your blood counts frequently for this side effect. If your white blood cell count declines to a level that raises concern, we will give you a medication called Filgrastim that increases white blood cell counts, and we will not give you PEGINTRON® until after your white blood cell count returns to a normal range.

PEGINTRON® has been associated with temporary decreases in CD4 cell numbers measured in the blood; it is likely that this apparent decrease is not the result of a direct toxic effect of PEGINTRON on CD4 cells. Instead it is more likely that PEGINTRON® causes the cells to reside in the tissues and not to circulate in the bloodstream. These changes in CD4 counts are temporary, and have not been associated with infectious complications; we plan to monitor CD4 cells during the study.

Risks of the Combination of Interferon Alpha 2b (PEGINTRON) and Antiretrovirals
We will monitor you closely for any potential drug interactions between PEGINTRON ® and other medications you may be taking. PEGINTRON ® has been commonly and safely used with antiretroviral medications.

Risks of Filgrastim (Granulocyte Colony Stimulating Factor, GCSF, Neupogen®)
If PEGINTRON causes too great a reduction in your neutrophil white blood cells, then we will give you Filgrastim.. Granulocyte colony stimulating factor (GCSF, Filgrastim) is a natural substance made by the body that stimulates the bone marrow to increase the number of neutrophils. Filgrastim is a synthetic form of GCSF that is FDA approved to increase neutrophils in individuals with severely low white blood cell counts, such as those with advanced HIV infection, individuals who have severe blood disorders, or individuals with fever and low white blood cell counts, such as those with cancer who are receiving chemotherapy. Filgrastim is an injectable medication that is commonly used, is generally very safe, and has been given to people with HIV infection including individuals receiving PEGINTRON. The most common side effect of Filgrastim is mild or moderate bone pain. Infrequently, Filgrastim can cause allergic symptoms, rash or injection site reactions, headache, nosebleeds, fever, nausea, and occasionally vomiting. Temporary increases in alkaline phosphatase, a blood test that is a marker of liver function have also occurred, but such changes have not been associated with disorders of the liver. Rarely, Filgrastim was associated with shortness of breath, which may be due to a respiratory distress syndrome, or a capillary leak syndrome of lungs. In very rare cases, rupture of the spleen has occurred. We will be monitoring you closely during this study to see if you will need Filgrastim and for the side effects of Filgrastim.

Apheresis
Apheresis is a procedure during which blood is taken from a vein in your arm. A special machine removes the white blood cells that are present in the blood specimen, and then returns all of the other blood components to you (via a vein in your arm). Thus, the only cells removed from your body by the apheresis procedure are white blood cells. Apheresis allows us to obtain sufficient numbers of lymphocytes to perform special studies.

The risks associated with apheresis procedures are primarily those of inserting an intravenous line (a catheter placed into a vein) and include discomfort at the site, occasionally bruising under the skin where the needle was placed, a tingling sensation during the procedure that can usually be relieved by chewing a calcium-containing antacid such as Tums®, the rare possibility of introducing infection, and possible fainting. Mild allergic reactions, including eye tearing, coughing, sneezing, itching, flushing, and hives may occur during apheresis and are caused by the chemicals used to sterilize the plastic collection kits. If you experience these symptoms, the donor room staff will give antihistamines, such as Benadryl, to you. The intravenous line infusing a saline solution will be kept in place during the manual apheresis procedure. Other uncommon side effects of the procedure include anxiety, chills, pain, and lightheadedness. There may also be a slightly increased bleeding tendency for a few hours after the procedure due to the temporary presence of the anticoagulant. In addition, on very rare occasions (less than 1 in every 1,000 times), malfunction of the leukapheresis machine can result in its failure to return all of your blood cells to you. In this case, the maximum amount of blood loss experienced is less than 450 milliliters (1 pint). Trained medical personnel who are equipped to deal with any of these potential problems are always on hand during the procedure. In addition, there are theoretical risks from re-infusion of the blood after

processing by the machine such as infection or an adverse reaction to the blood components. However, these risks must be exceedingly rare if they occur, since they have not been seen in many thousands of volunteers who have undergone this or similar procedures to date. Rarely the performance of frequent apheresis procedures over a short period of time can result in a drop in total lymphocyte counts, including the absolute CD4+ T cell count, or a drop in the platelet count (platelets are the blood cells that help your blood to clot). The extent or duration of the drop in these counts may be unpredictable and vary from person to person, although we plan to monitor your counts during participation so that this is less likely to occur. The short or long-term risks associated with these drops are also unknown, although possibly could be more serious in those individuals whose baseline counts are already below the normal range as a result of HIV-1 infection or other medical conditions. Based upon your CD4 cell count or other medical conditions, we may limit the number of times that you are eligible to undergo apheresis over a set period of time, and may require that these or other safety blood studies be performed and checked periodically during the time that you are enrolled on this protocol.

REASONS FOR REMOVING YOU FROM THE STUDY WITHOUT YOUR CONSENT
You may be removed from the study without your consent for the following reasons:

- The NIH doctor feels that staying in the study is harmful to you
- You don't keep your appointments
- The study is cancelled or stopped

Cost
There will be no charge to you or your health insurance company for any of the costs which are directly related to this study. However, the costs of any other medical care outside of this study during this period will be your responsibility.

Alternatives
This study provides no benefit and the alternative to participating is not participating

New Findings
You will be told of any new information learned during the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when the overall results of the study may be available.

Remuneration
There is monetary compensation for time, inconvenience, and for certain procedures. You will receive payment at the end of the study; you will receive $40 for each visit, and $100 for the apheresis. As a result, you can receive up to $760 for the entire study.

Conflicts of Interest
The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process http://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf. You may ask your research team for additional information or a copy of the Protocol Review Guide. This protocol may have investigators who are not NIH employees. Non-NIH investigators are expected to adhere to the principles of the Protocol Review Guide but are not required to report their personal financial holdings to the NIH.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and 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 authorized hospital accreditation organizations.

2. 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.

3. Payments. 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.

4. 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, Dr. Frank Maldarelli, Building 10, Room, 5A06, Telephone301.435.8019. You may also call the Clinical Center Patient Representative at (301) 496-2626.

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

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 JUNE 15, 2015 THROUGH JUNE 14, 2016.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____