A Randomized Placebo- Controlled Trial Of Recombinant Human Interleukin- 11 Inhuman Immunodeficiency Virus -Positive Patients With Thrombocytopenia

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A. Study Purpose

Thrombocytopenia is a common hematologic manifestation seen in Human Immunodeficiency Virus (HIV) - positive patients. In Acquired Immune Deficiency Syndrome (AIDS) patients it is proposed that between 25-45% of patients have thrombocytopenia (1). Thrombocytopenia may result in minor bleeding episodes such as nose or gum bleeding, and easy bruising. However it has also been reported in a study following HIV-related thrombocytopenia, in patients with platelet counts < 30,000 to be responsible for three major bleeding episodes including menorrhagia and gastrointestinal bleeding (2). Thrombocytopenia has also been reported in the HIV patients to have resulted in more serious events as Intracranial hemorrhage (3).

The mechanism of HIV-related thrombocytopenia has been postulated to be due decreased platelet production and survival (4), decreased numbers of megakaryocyte progenitors (5,6), increased splenic platelet sequestration (7), and increased amounts of immune complexes(8,9). In a recently published article (10), the investigators measured peripheral platelet mass turnover, circulating levels of thrombopoietin, platelet thrombopoietin receptor number, and serum antiplatelet glycoprotein IIIa antibody, an antibody associated with HIV related thrombocytopenia, to determine the etiology of thrombocytopenia in HIV patients. The results of the study concluded HIV related thrombocytopenia is related to ineffective platelet production, despite increased thrombopoietin production and increased megakaryocyte mass. Other etiologies may include shortened peripheral platelet life span with increased splenic sequestration.

Presently there is no standard of care for HIV-related thrombocytopenia. Spontaneous remission of thrombocytopenia is reported to occur in 10-20% of HIV-positive patients with thrombocytopenia (11). Other treatments include corticosteroids (12), zidovudine (13), splenectomy (14), intravenous immune globulin for acute events (15), and anti-rhesus D immunoglobulin (16,17). In non-human models, pegylated recombinant human megakaryocyte growth and development factor has been shown to increase platelet counts in HIV- infected chimpanzees without increasing HIV replication (18). Present treatment options are either experimental, quite expensive, used optimally only in the acute setting, or have questionable effects on viral replication and immunosuppression with long term use. Research is on going in this field for an effective chronic treatment for this problem.

Recently interleukin -11 was approved and is being used for prevention of chemotherapy induced thrombocytopenia. Interleukin -11 (IL- 11) is measurable in a wide number of human tissues (19). IL- 11 stimulates proliferation of primitive stem cells and progenitor cells in the hematopoietic system synergistically with other cytokines to become further committed progenitor cells (20). IL- 11 in vivo produces increased megakaryocytopoeisis in humans with increase in production, differentiation and maturation of megakaryocytes (21,22). This is evidence by increase in megakaryocyte number and ploidy in vivo (22). IL- 11 is well tolerated in humans with minimal and transient side effects (2 1). In a randomized placebo control trial using IL-11 at the current recommended dose of 5 0 micrograms/kg, 30% showed no need for platelet transfusion where only 4 % in the placebo group(23) in oncology patients after myelosuppressive chemotherapy. In another randomized placebo trial of a similar patient population, using recombinant human interleukin-11 with intent-to-treat had a 68% response to the drug, requiring no transfusion compared with 41 % of the placebo group(24).

Our study is designed to address if IL- 11 has an therapeutic effect on HIV-related thrombocytopenia. If IL-11 does have a therapeutic effect, is it on any particular etiology of

thrombocytopenia associated with HIV. We would also like to look at in vivo if IL-11 causes any increase in viral replication.

B. Study Design

Patients will be randomly assigned using a random block format to receive recombinant human interleukin- 11 at a dose of 50micrograms/kilogram/day or placebo subcutaneously. Administration of the drug was done in a blinded fashion such that the patient, investigator, and study sponsor were not able to identify the identity of the medication. A nurse was trained to give the subcutaneous injections as well as train the patient and /or a partner how to give the injections. The patients received the injections during the first seven days in the clinic setting and then monitored daily during self injection for the duration of the therapy. The drug was given for up to 21 days consecutively. Blood counts were obtained three times a week for the duration of the use of the drug. Viral loads were obtained at the end of weeks one and three.

Subjects could stop the drug after 10 days if their platelet count was >60,000/microliter. Subjects would otherwise continue the injections until their platelet count was >60,000 or for the full 21 days.

Other end points of the study include a two fold log increase in viral load during treatment. If the subject was found to have an increase in their viral load, the injections would be discontinued. Viral load would be followed in patients at the one and three month mark. Complete blood counts will be taken three times a week while the patient is receiving the injections and then at four and six weeks, two and three months.

Transfusions would be given if the platelet count was <10,000 /dl or the patient was clinically bleeding and medically indicated as per the decision of the physician.

Subjects may be withdraw from the study at anytime if they feel it is not in their best interest to participate. Patients can also be withdrawn from the study if for pregnancy, required treatment with aspirin or anticoagulants.

The primary end point of the trial is a platelet count >60,000. It will then be %.01 determined by using Fisher's exact test for the data. The subjects will be recruited from the HIV clinics of the New York-Presbyterian Hospitals. The subjects will be identified and approached by their physicians. The population serviced in the HIV clinics of the participating hospitals has a patient population that will include minority groups to be well represented in this study.

a. Inclusion criteria for the study is as follows;

1. documented HIV seropositivity
2. men and women greater than 18 years of age
3. negative human BCG test
4. undetectable viral load serologies for 3 months
5. stable antiviral regimen of the physicians choice
6. platelet count of <30,000 for two consecutive serum counts over a two week period
7. hemoglobin count > 9g/dl
8. adequate cardiac, renal coagulation and liver function serum tests

b. Exclusion criteria

1. history of active bleeding
2. previously history of congestive heart failure
3. history of atrial arrhythmias
4. use of aspirin or anticoagulants
5. current infection
6. previous platelet transfusion in the last three months

In this study with a 10-20% spontaneous response rate (11) and a documented response between 30-68%(23,24) using a power of 80% and a type 1 error of .05 we will need to recruit 120 people to show a difference between 15% for placebo and 30% rhIL-11. The CPMC clinic having -900 patients, 600 return regularly. It is estimated that 35% of these patients have undetectable viral loads. It is also

hypothesized that approximately one third of all HIV- positive patients will be thrombocytopenic at some point in their disease (1). Using these percentages the recruitment from CPMC clinic would be approximately 73 patients per year. The New York Hospital clinic is estimated to have an equal if not increased patient population in terms of visits per year. It is estimated that it could take approximately eighteen months to recruit patients for this study.

C. Miscellaneous

a. Study Procedures included in the study for eligibility are:
- Complete medical history
- Electrocardiogram
- Physical examination including pulse, blood pressure,
- CBC,
- platelet count
- viral load
- Beta hCG

b. Procedures during the study include:
- Bone marrow aspiration and biopsy
- CBC,
- platelet count
- viral load
- Serum antiplatelet glycoprotein IIIa antibody
- subcutaneous injections Hepatitis C Antibody

c. Procedures after the study
- CBC,
- platelet count
- viral load

Venous blood drawing will be with aseptic technique in the antecubital fossa. Risks of this procedure include minimal discomfort, pain, ecchymosis (bruising), and a minimal chance of hematoma or phlebitis (infection of the vein). A bone marrow aspirate and biopsy will occur in the posterior ileac spine. The patient will be prepped with betadine and draped. The patient will be injected with lidocaine for anesthesia. A Jamshidi needle will then be used to obtain the aspirate and biopsy by puncturing the posterior superior ileac spine of the patient with some amount of pressure. Once within the bone the physician will aspirate the bone marrow. Then with a twisting motion, the physician will obtain the bone marrow biopsy. Risks involved with the procedure include if the needle were to break of in the patient's bone, surgical removal would be necessary, osteomyelitis, pain and tenderness at the site, and minor bleeding or hematoma at the site.

D. Study Drugs

Recombinant human IL-11 (rhIL-11), (Neumega a registered trademark of Genetics Institute) will be used in this study. Neumega is derived from genetically altered Escherichia coh. The effects of which have been studied on animal and human subjects with bone marrow suppression secondary to chemotherapeutic agents. The drug is presently undergoing trials in animal models for safety with respect to the HIV positive patient.

The known side effects of rhIL-11 in human subjects include fluid retention. Patients may experience mild to moderate dyspnea on exertion or peripheral edema. There may also be an increase in previous fluid collections, i.e. pleural effusions and ascites. There may be mild decreases in hematocrit thought to be related to the increase in plasma volume (dilutional anemia) that is reversible with discontinuation of the drug. It should be used with caution in people with congestive heart failure. Deaths

have occurred with patients taking rhIL-11 secondary to severe hypokalemia when taken with diuretic therapy. Electrolytes need to be monitored carefully with patients using both therapies.

rhIL-11 has been shown to produce transient atrial fibrillation in 10% of patients while on the drug. The arrhythmia is thought to be secondary to the increased fluid retention. rhIL-11 has not been shown to be directly proarrhythmogenic. No ventricular arrhythmias have been associated with rhIL-11.

Patients taking rhIL-11 has also been found to experience transient blurry vision and have been found to have papiledema that resolves with discontinuation of the drug. This is not associated with inflammation.

The treatment with rhIL- 11 will be a subcutaneous injection daily for 28 days on a outpatient basis.

E. Medical Devices

No medical devices will be used in this study.

F. Study Questionnaire

No questionnaires will be used in this study.

G. Confidentiality of Study Data

All study data will be coded (without any personal identifiers) and will be stored in a location accessible only to the investigators. The research records are confidential. The study publication will not reflect the names or other identifying information. Medical personnel working with the US Food and Drug Administration and Genetics Institute, Inc. will have access to the patients medical records but will maintain confidentiality throughout the study.

H. Location of Study

The study will be conducted in the clinical care areas of the New York -Presbyterian Hospitals HIV clinics. Injection of medications and transfusions will be provided at the Milstein or New York Hospital locations.

I. Risks and Benefits

a. Risks

The risks are described in the study drug about the use of rhIL-11. The risks of the procedures are described in the study procedure section.

b. Benefits

The patient may or may not directly benefit. There is no way presently to determine which patients will respond to the IL-11with increase in their platelet counts. The benefits may include improvement in platelet counts and decrease in major or minor bleeding episodes. Improvement will also decrease the risk of significant or life threatening bleeding events. We will also learn more about the role of IL- 11 in the HIV positive patient.

J. Alternative Therapies

Alternative therapies for thrombocytopenia in the HIV positive patient are many. The patients being studied will be transfused if their platelet counts are below 15,000 at anytime during the study. Presently there is no particular standard of care used for HIV related thrombocytopenia.

K. Compensation and Costs to Subjects

The patient will not be compensated for their participation in this study. The lab work for inclusion criteria to the study will be at the expense of the patient. The CBCs, viral load studies, bone marrow procedure and interpretation will be paid for by the sponsoring drug company pending proposal approval.

Secondary to the invasiveness of the inclusions criteria, the subjects will be compensated for the bone marrow portion. The patients will receive half of the payment on the date of the procedure and the other half either on completion, on completion, on reaching an endpoint, or upon voluntary removal of oneself from the study.

L. Minors and Research Subjects

No minors will be entered into this study.

M. Radiation or Radioactive Substances

No radiation or radioactive substances will be used in this study.

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