Placebo Controlled Trial of Selenium in HIV Cardiomyopathy

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A. Study purpose and Rationale

The purpose of this trial is to study the role of antioxidant deficiency, selenium in particular, on the development of HIV dilated cardiomyopathy and the effect of selenium repletion on the progression of the disease.

Patients with HIV frequently suffer from weight loss and severe protein-calorie malnutrition. Nutritional deficiencies may significantly impair immune responses and other organ functions and have a significant impact on HIV-1 related morbidity and mortality . [2]

Patients infected with HIV type I have been reported to be deficient in selenium. [3,4] Selenium functions primarily in the form of selenoproteins [10] one of them, glutathione peroxidase, catalyzes the reduction of peroxides that can damage cells and tissues. This micronutrient is therefore and integral part of the antioxidant defense system.

Gewirtz et al demonstrated a significant selenium deficiency in his study population of 52 HIV patients with CD4 less than 400 (100% prevalence). After one year of supplementation, median values of plasma selenium returned to above normal[5] Similarly, Delmas-Beauvieux studied 45 patients with unknown CD4 counts and demonstrated lower baseline selenium levels in all her HIV than those in healthy controls. After repletion, selenium values doubled between baseline and 12 months. Overall most studies report about 30-50% prevalence of selenium deficiency in all HIV infected patients, and 80-100% prevalence in patients with CD4 counts below 400. [1-9]

A weakened antioxidant defense system appears to play an important role in the increased oxidative stress seen among patients with HIV-1. Greater lipid peroxidation and lower plasma concentrations of selenium were observed in patients with HIV-1 who had no active opportunistic infection, compared with age-matched seronegative control subjects.[11] Some investigators have suggested that selenium deficiency is strongly associated with decreased survival in HIV –1 disease.[2] It has been postulated that in patients with HIV infection, selenium deficiency may be due to the trapping of selenium by a selenoprotein encoded by the proviral genome.[6]

Diminished selenium levels have been associated with anemia, congestive cardiomyopathy, skeletal muscle myopathy, and increased cancer risk. From that one can deduce that HIV positive patients are clearly at high risk for these conditions. It would be of benefit to clarify the contribution of this deficiency to their progressive downhill natural history of AIDS and progression of the above conditions.

Cardiac involvement is not often recognized during the course of HIV infection as it is often attributed to dysfunction in other organ systems. And yet dilated cardiomyopathy in HIV is associated with poor prognosis; the median survival is 101 days, as compared with 472 days in patients with normal hearts who are at the same stage of disease.[15]

Studies of LV dysfunction in these patients have reporded a wide ranges in prevalence, with the number of cases rising in patients with CD4 counts < 400. The prevalence ranges 14% in all comers, to 30-40% [13,19-21] in patients with decreasing CD4 counts (below 400). More importantly, about 67% of them do not have any clinical symptoms. In some studies subclinical cardiac abnormalities are persistent and often progressive In a pooled analysis of Echo studies reporting on asymptomatic LV dysfunction, about 6% eventually developed CHF when followed for 18 months.[14]

Barbaro et al presented a large prospective study of the incidence of dilated cardiomypathy in asymptomatic HIV-infected patients (CD4>400 and normal baseline Echoes (55+/-5.2)). The result of their study is consistent with others that indicate that cardiac involvement usually occurs during the late stages of HIV infection, when the immunologic system is clearly compromised. [12]

In another study Barbaro et al studied 1236 patients with CD4 above 600 not on ART and showed that over 50% of them had a reduction in 19.7% in EF as compared to healthy subjects (in HIV infected patients the mean EF was 47.6 +/- 9.1 as compared to 59.3+/-7.4 $p<0.001$). [18]

The most common findings in HIV-infected patients are a tendency towards dilatation of the cardiac chambers and reduced contractility.

Not much is known about the mechanism of HIV-related heart disease. Possibilities include direct infection and injury of myocytes, toxicity due to cytokines generated as a result of cardiac disease or viral proteins. Co-infection with other cardiotropic viruses, cardiotoxicity as a result of antiretroviral therapy or illicit drug use, and nutritional deficiencies.[15]

Luginbuhl et al have shown that malnutrition and wasting are important independent predictors of cardiac-related morbidity and mortality. [16] Precise effects of malnutrition is not known; it is unclear what degree of selenium deficiency can cause ventricular dysfunction or whether there are other synergistic clinical effects . For example low levels of selenium or other micronutrients have been reported to increase the ability of Coxsackie's virus to cause cardiac damage and to increase the toxic effects of zidovudine on skeletal muscle. [15,17]

Nutritional status should be assessed as part of overall evaluation of ventricular function since many clinical factors can influence ventricular function in HIV-infected patients and a deficiency may become a potentially treatable cause of cardiomyopathy. If abnormalities are diagnosed sufficiently early, preventive and therapeutic strategies can be applied.

In human beings, an association between low selenium status and Keshan disease, a cardiomyopathy endemic to parts of China, was documented over 20 years ago. This type of dilated cardiomyopathy was related to selenium deficiency, for its incidence matched the distribution of selenium deficient areas, and a prospective placebo controlled study has shown that prophylactic administration of sodium selenite prevented new cases of the disease. [22] Similarly, two small interventional studies of selenium deficient HIV patients with impaired cardiac function have documented improvement in their EF after supplementation. Yet neither study was blinded, controlled or large enough to document a reproducible effect of the effect of supplementation. [23,6]

Epidemiologic studies have shown that cardiomyopathy secondary to selenium deficiency may be prevented with selenium supplementation, but the response to supplementation after cardiomyopathy has developed is less clear. Functional improvement may be possible in early selenium deficiency but not in advanced disease .

Although selenium deficiency is rare, loss of its antioxidant protection may exacerbate damage from other disease-causing factors. A double-blinded, placebo controlled trial will be undertaken to establish a relationship between correction of selenium deficiency and progression of cardiomyopathy. It is proposed in this study that while a meaningful recovery may not be demonstrated, a significant retardation of the progression of cardiomyopathy will be possible.

B. Study Design and Statistical Analysis

Hypothesis: Selenium supplements administered to HIV- positive, selenium deficient patients with depressed ejection fractions, will slow down or reverse the cardiac dysfunction as compared to the placebo group.

The study will require a total of 172 patients, who will be randomly assigned to selenium or to placebo in a double-blinded study. The treatment group and control group each involves 86 patients with HIV and selenium deficiency. These patients will then be followed for 12 month with primary endpoint being change in the EF.

The number of patients required in each group is 54, is based on a power of 80% , alpha 0.005 and mean difference of at least 5% in the values of EF between baseline and treatment group. This is based on observational studies of impairment of systolic function in HIV patients with CD4 below and above 400. Additional patients will be recruited to each group to account for a 20% drop out rate in each group and a 40% prevalence of cardiomyopathy.

Primary endpoint will be the change in Ejection Fraction over the course of 12 months.The levels of selenium in both groups will also be recorded to document an appropriate response to supplementation, and to document compliance with the protocol. In addition, the activity of glutathione peroxidase will be documented at baseline and at the 12 month endpoint to record a functional parameter of selenium status. Patient's response to selenium intervention or his/her usually dietary practices will be monitored via measurement of glutathione peroxidase activity , both decrease in response to selenium deficiency.

Change in EF in each patient will be documented and the method of data analysis will be a t-test statistical analysis to compare the mean of the change in EF in each patient in both groups. Mean selenium levels between placebo and selenium group will also be compared using a t-test.

Every patient in both arms of the study will be evaluated with the intention to treat analysis.

C. Study Procedure

The study will recruit patients who are HIV-1 positive, with a CD4 count between 400 and 50 cells/mm3 and selenium deficiency reported as plasma selenium concentration less of than 85 mcg/L.

Patients will fill out a questionnaire regarding their dietary practices, medications, and alcohol, tobacco history. They will be evaluated by a nutritionist.

Patients will be randomized into two groups, one will receive placebo, the other, 500 mcg of selenium per day for one year. .

They will have Echo checked at baseline and after three, six, and twelve months. Ejection fraction and LV volumes will be recorded. Definition of cardiomyopathy will include EF<= 45%. Lower limit of normal 50%. At that same time they will also have their selenium level checked. At the end and the beginning of the study, toenail clippings will be collected again to document selenium intake and levels over the study period. In addition, the activity of glutathione peroxidase will be documented at baseline and at the 12 month endpoint to record a functional parameter of selenium status.

To ensure reproducibility of measurements, patients will be brought back at each entry point to recheck their Echo and selenium level.

The Echo will be performed in the Echo lab by the same technician and interpreted by the same reader.

Selenium levels will be determined by a standardized fluorometric method, with selenium reference obtained from the National Institute of Standards and Technology; measurements of less than 85 mcg/L will be considered deficient (2). Selenium levels will also be measured in toenail clippings of the subjects to reflect selenium intake for the past 6-12 months. Glutathione peroxidase activity will be determined as described in Delmas-Beauvieus, et al. (7)

D. Study Drugs

Sodium selenite, 400-mcg tablet administered daily.

Sodium selenite is the chemical formula of choice for selenium, one of the major antioxidants in the human body. Selenium functions primarily in the form of selenoproteins (10) Selenium functions primarily in the form of selenoproteins, one of them, glutathione peroxidase, catalyzes the reduction of peroxides that can damage cells and tissues. Other selenoproteins provide an oxidant defense. Selenium, therefore, as part of glutathione peroxidase, is considered one of the antioxidant nutrients (like Vit E, iron, zinc and copper), which help prevent generation of free radicals and decrease the risk of oxidative damage to DNA. proteins, lipids. (10)

Cellular and plasma glutathione peroxidase are the main functional parameters used for assessment of long and short-term selenium status, respectively. Selenium concentration in blood and toenails are accurate in assessing dietary intake. Selenium in toenails reflects selenium intake or the past 6 to 12 months. Plasma selenium concentration approximates acute selenium status while red blood cell content approximates long-term selenium status, approximately 120 days.

Dietary recommendations of 70mcg/day for men and 55mcg./dayfor women were intended to be adequate for maintenance of glutathione peroxidase activity.

Selenium is found in greatest concentration in meats, seafood, grain and seeds (depending on the content of the soils in which they were grown) and enteral formulas are currently supplemented with selenium, ensure contains 76mcg/L.

The functions of selenium are poorly understood but it has been postulated that it is required for immune functions lymphocyte proliferation, macrophage function, and natural killer activity.

Diminished selenium levels have been associated with sterility (10), anemia, congestive cardiomyopathy, skeletal muscle myopathy, and increased cancer risk.

Selenium toxicity (appear in people taking 750-850 mcg/day) manifests itself as changes in skin, hair and nail, loss of teeth, weight loss. Seizures, depression, ataxia, blindness, fatigue in more severe cases.

E. Medical Devices

None

F. Study questionnaires

The questionnaire will identify patient's age, race, sex, medications, tobacco and alcohol history, risk factors for HIV, history of drug use.

G. Study subjects

General characteristics: patients will be enrolled over a 3 month period. Eligible patients are men and women age 18-65 with HIV for 6 months or more. CD4 counts 400 to 50 cells/mmm3, and selenium below 85mcg/L.

Exclusion Criteria: Prior history of coronary artery disease,

Previous congenital or acquired heart disease, family history of dilated cardiomyopathy or MI<45y.o, personal history of diabetes or hypertension, Rheumatic disease, previous use of both micronutrient supplements and Ensure products for longer than 6 months.

H. Recruitment of Subjects

The individuals will be recruited from the HIV clinic at CPMC where a total of about 900 patients is seen is registered. Of these 90% have CD4 counts below 400 on or off medications. It is estimated that of these at least 50% will have selenium deficiency.

Thus, this database can be used to identify potential subjects in the last five years using the computer database and charts (810 patients) with selenium deficiency (405). This does not account for new patients seen in the clinic at a rate of 2-3 per week, as per the nutritionist.

I. Confidentiality of Study Data

Patients will be coded by a number of entry and their information will be kept strictly confidential.

J. Conflict of Interest

None

K. Potential Risks to the Patient during Study Protocol

Very minimal potential of selenium toxicity, not seen at the doses used in this study.

L. Potential Benefit

Screening for incidence of cardiomyopathy with the possibility of initiation of conventional therapies if they develop symptomatic CHF. Potential for reversing or slowing down the progression of cardiac dysfunction with selenium supplements.

M. Alternative therapies

Conventional (ACEI, Digoxin, Lasix) therapies for CHF in symptomatic patients.

N. Compensation to Subjects

None.

O. Cost to Subjects

None, supplements will be provided by the study.

P. Minors as Research Subjects

None.

Q. Radiation or Radioactive Substances

None.

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