Clinical Determinants of Immune Reconstitution Syndrome in Dominican AIDS Patients after the initiation of Highly Active Antiretroviral Therapy

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A. Introduction

The use of highly active antiretroviral therapy (HAART) for patients with AIDS has resulted in significantly decreased mortality as well as a large reduction in morbidity associated with opportunistic infections. However, increasing numbers of case reports and case series since the late 1990s have identified a subset of patients who paradoxically develop opportunistic infections after initiating HAART and with reconstitution of their immune systems as measured by CD4 lymphocyte counts. This phenomenon has been referred to in the literature as immune reconstitution syndrome, immune restoration inflammatory syndrome, or most commonly immune reconstitution inflammatory syndrome (IRIS).

The presumed mechanism of this clinical phenomenon is that AIDS patients have latent infections with opportunistic organisms to which the immune system does not mount an inflammatory response because of immunosupression. When the immune system is reconstituted after the initiation of HAART, an inflammatory response ensues and often there is a dramatic presentation of opportunistic infection. Reports in the medical literature describe this phenomenon with multiple different organisms including Pneumocystis carinii, Mycobacterium avium complex, mycobacterium tuberculosis, Cryptococcus neoformans, cytomegalovirus and others.

Limitations of the medical literature to date have included an absence of well designed prospective studies, as well as the absence of a uniform case definition. A particular problem for the systematic study of this syndrome is the difficulty in objectively distinguishing IRIS from intercurrent infection with opportunistic infection in late stage AIDS patients.

The government of the Dominican Republic began a public sector AIDS treatment program, termed the Unidad de Coordinacion en Accion Integral (UCAI), in November, 2003 with the goal of providing adequate and comprehensive treatment to AIDS patients including HAART. To date this program has started 590 patients on HAART. Greater than 95% of these patients were started with a known CD4 count of 250 or less. Projected enrollment in HAART treatment is 2000 patients over the next two years. These patients are antiretroviral naïve and will be followed through a clinic system including physicians, nurses, educators and adherence workers.

B. Study Purpose and Rationale

This study will prospectively enroll HIV+, antiretroviral naïve patients starting HAART through UCAI. These patients will be sorted into two cohorts those who have an intial CD4 count less than 100 and those who have an initial CD4 count greater than 200.

These patients will be followed closely and clinical, virologic, immunologic and adherence factors will be monitored. The primary outcome will be the development of opportunistic infections within a specified time period. The medical literature supports the idea that IRIS develops predominantly among patients with nadir CD4 counts less than 100. As well the presumed mechanism of IRIS: latent infection and reconstituted inflammatory response would occur only in those patients who are sufficiently immunosupressed that they will be unable to mount an appropriate inflammatory response.

C. Methods

a. Subject Selection

A prospective cohort study of antiretroviral naïve, adult HIV+ Dominican patients accrued through the 11 clinical sites through which the UCAI program operates. Written informed consent in Spanish will be obtained form each subject. There will be two separate wings: those with CD4 count greater than 200 and those with CD4 counts less than 100 at the initiation of HAART. Both groups will receive standard of care therapy. Patients will be excluded if they are unable to consent to the study, age less than 18, are taking medications which interact with HAART, have a current opportunistic infection, or patients with a known prior CD4 nadir of less than 200 who have subsequently recovered their CD4 count to greater than 200. The study period will be from two weeks after the initiation of HAART until 4 months after the initiation of HAART. The rationale for this time period is based on the medical literature as well as our understanding of the tempo of immune reconstitution after HAART. Based on a prior chart review it is estimated that the two cohorts will accrue at a rate of 2 to 1; that is two patients with CD4 counts less than 100 for every one patient with CD4 count greater than 200. Patients will have baseline CD4, viral load testing, an education session, and physical exam. Thereafter patients will be seen by their clinic doctor every two weeks, at this time CD4 counts will be obtained as well as any other tests the clinic physician believes necessary. At 4 weeks cytokine levels including interferon gamma, IL-20 will be drawn on all patients. Complete demographic and adherence data will be collected.

b. Statistical Analysis

The study will be 90% powered to detect a difference between the two groups. Based on literature review it is estimated that approximately 10% of the subjects with CD4 counts less than 100 will develop an OI during the study period as compared to 2% of the patients with CD4 counts greater than 200. Based on these assumptions and the differential rate of accrual between the groups it is estimated that we will need 144 patients in the group with CD4 counts greater than 200 and 287 patients in the group with CD4 counts less than 100.

Chi-squared tests will be used to compare the proportion of patients in each group with OIs. T-tests will be used to analyse adherence rates and change in CD4 count. Multivariable logistic analysis using demographic, adherence and cytokine data will be performed.

The primary outcome will be development of opportunistic infections in each group. The outcome that is tentatively expected will be that the two groups have proportionately similar increases in their CD4 counts but dissimilar rates of opportunistic infections.

Secondary outcomes will include rates of CD4 change, levels of cytokines, adherence and there association with development of opportunistic infection.

D. Study Drugs

None

E. Medical Devices

None

F. Study Questionnaires

Demographic data including gender, age, education level, past medical history will be collected in an anonymous and confidential manner.

G. Confidentiality of Study Data

All study data will be collected in a confidential and anonymous manner and assigned a unique random identifying number.

Records of identifying numbers will be stored in a secure central location accessible only to investigators.

H. Potential Conflict of Interest

None.

I. Location of Study

The study will be carried out at 11 UCAI clinics located in the Dominican Republic.

J. Potential Risks

No additional risk to the subjects beyond the risks associated with venopuncture.

K. Potential Benefits

Since all patients will be receiving standard therapy including prophylaxis against OIs there would be no expected benefit beyond the increased surveillance associated with a study environment.

L. Alternative Therapies

None

M. Compensation to Subjects

None

N. Costs to Subjects

None

O. Minors as Research Subjects

None

P. Radiation or Radioactive Substances

Not Applicable

Q. References

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