NATAP FORUM

Current Issues in HIV Treatment: NATAP's Fifth Continuing Education Symposium

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Thymus Transplant Research for HIV and Its Potential for Immune Reconstitution

by Louise Markert, MD

In HIV-seropositive adults, highly active antiretroviral combination therapy leads to dramatic drops in plasma HIV RNA and increases in CD4 T cell counts. A question that arises is: Does the increase in CD4 T cell counts represent an increase in numbers of T cells or, more importantly, does it also represent an increase in CD4 T cell functions?

Our concern arises because, in HIV infection, with the death of CD4 T cells, the T cell repertoire becomes restricted. When patients with restricted T cell repertoires are treated with combination antiretroviral therapy, we want to know whether the T cells that develop represent more cells with the same restricted repertoire or whether the T cell repoertoires has expanded.

In discussions of CD4 T cell repertoire and function, the thymus is an important topic. The thymus is the organ which creates the original broad repertoire of T-cells. Drs. haynes and Hale at Duke have shown that the thymus remains active creating new T-cells long into adult life. They also have shown that the thymus is damaged in HIV infection. We do not know whether the lack of functional thymus will prevent development of a broad T-cell repertoire in HIV patients. We are addressing this issue by transplanting thymic tissue into HIV patients and then following T-cell function.

Of pivotal importance in this study is our assessment of CD4 T-cell function. We are assessing T-cell function by testing the ability of T-cells to respond to the neoantigen, keyhole limpet hemocyanin (KLH). This aspect of the study is novel; we have an IND to do these immunizations. We are assessing the function of the thymic transplants directly by biopsy at 2 and 6 months.

The background for this project is based on results from an NIH-funded General Clincial Research Center Study entitled "Thymic Transplantation in Complete DiGeorge Syndrome." In complete DiGeorge syndrome, patients have no T-cells and no T-cell function secondary to thymic aplasia. We have transplanted 2 patients with complete DiGeorge syndrome. Both patients achieved good T-cell function.

We have enrolled 8 HIV-seropositive patients with 200 to 500 CD4 T cells, who have hd less than 6 months of monotherapy. Thy did not have any protease inhibitor therapy. During screening, baseline studies are conducted including flow cytometry, T-cell proliferative studies, and plasma HIV RNA. A lymph node biopsy is done to assess tissue HIV RNA. After screening, the patients are started on ritonavir, ZDV, and 3TC, which they take for the next 2 years. The key procedure done 1 week after starting combination therapy is immunization with KLH and tetanus to assess responses to neoantigens and recall antigens. These immunizations are repeated every 6 months thereafter. At the end of the first 6 weeks (42 days) of combination antiretroviral therapy,

the patients are randomized eith to receive a thymic transplant or to be in the control group. On day 42, all patients hae a hymph node biopsy to assess viral burden in the tissue. One half of the patients receive a thymic transplant. The patients' thymus transplants are biopsied 2 and 6 months later. All patients receive a lymph noe biopsy at 6 months.

The primary hypothesis being tested is that CD4 T cell counts will increase more in thymic transplant patients than in control patients who are on combination antiretroviral therapy. A secondary hypothesis is that T cell function will improve more in thymic transplant patients than in control patients. An additional secondary hypothesis is that thymic transplants will not be rejected.

Preliminary data from the trial shows that approximately one fourth of the patients do not develop responses to neoantigens after 1 year of combination antiretroviral therapy. Also, patients who begin therapy with 200 or 500 CD4 cells have enough immune function to reject thymus grafts.

Because of the finding of graft rejection, we are now asking if graft rejection would occur in patients with very low CD4 coutns. We have recently obtained IRB, GCRC, and FDA approval to study 2 patients with CD4 coutns <50, despite 6 months of combination antiretroviral therapy. We will match one DR allele because even the most frequent would only occur in 1 in 5 thymuses. It is not practical to try to match more alleles because of the low frequency of HLA-DR alleles. The patients will be given 2 doses of ATG to try to prevent graft rejection. The ATG that we will use will be 30mg/kg given after the transplant. This should lead to temporary immunosuppression.

We, of course, are very sensitive to the potential problems of immunosuppression in this group of patients. We will select patients who will have the least risk of encountering infectious problems secondary to the ATG. Monthly screening evaluations will be done for cytomegalovirus, Epstein-Barr virus, Mycobacterium, and Kaposi's sarcoma.

In the study, plasma HIV RNA and CD4 T-cell counts will be followed closely. KLH and tetanus immunizations will be done every 6 months, as in the parent protocol. Two doses of ATG (30mg/kg) will be given after the transplant. The thyumic biopsies at 3 and 6 months will be assessed for rejection by monoclonal antibody staining. After obtaining the results from the substudy, we will modify our initial study to evaluate a more appropriate group of patients with and without thymic transplantation, and with and without ATG. We will continue to evaluate the ability of HIV seropositive patients to respond to neoantigens. Lastly, we will extend these studies to thte pediatric population.

Lectures and addresses at the Janaury 17th Forum included:

Jules Levin, Executive Director of NATAP - Welcoming Address
Dr. Robert Siliciano, MD - HIV in the Lymph Tissue and Latent Long-lasting Virus in T-Cells (CD4s).
Dr. Justin McArthur, MBBS, MPH - The Brain, HIV, and the Effect of New Treatments
Dr. Carl Fichtenbaum, MD - Treatment and Prophylaxis for Opportunistic Infections in the New Potent Therapy Era. Can Prophylaxis or Maintenance Therapy Be

Discontinued?
Dr. Louise Markert, Thymus Transplant Research for HIV and Its Potential for Immune Reconstitution