

Contact: Jonathan Weil
jweil@med.cornell.edu

Embargoed until November 27, 2000

Weill Cornell Studies Reveal Accelerated Improvement of Immune System &
Antiviral Reactivity in Chronic HIV Infection
--Low Daily Doses of Interleukin 2 May Hold Key to Management of HIV Infection--

New York, NY (November 13, 2000) -- A multicenter controlled study -- led by Dr. Kendall Smith, Chief of Immunology at Weill Medical College of Cornell University in New York -- has shown that low daily doses of the T cell growth factor Interleukin 2 (IL2) can be given to individuals with chronic HIV infection and low lymphocyte concentrations for as long as six months without severe side effects, resulting in accelerated improvement of the immune system.

In another study, Dr. Smith and his team of researchers at Weill Cornell have uncovered evidence that individuals with chronic HIV infection, who have received antivirals plus IL2 and have achieved elevated concentrations of circulating killer lymphocytes, can mount significant control of the level of HIV detectable in the blood.

Two separate reports detailing these findings are to appear in the November 2000 issue of the journal *HIV Clinical Trials*.

Almost all individuals infected with HIV do not know when they became infected, so that usually the virus becomes established as a chronic infection before any antiviral therapy can be initiated. Unfortunately, HIV damages the immune system early during the course of infection, so that even if effective antiviral therapy is administered, the antiviral drugs cannot cure the infection, and when they are discontinued, the virus reappears within a few weeks. Consequently, the antiviral drugs have to be

(More)

taken continuously to avoid a viral relapse. However, with such chronic administration, the antiviral drugs cause serious side effects, such as elevated blood cholesterol and sugar, often necessitating their discontinuation.

Dr. Smith and his research team discovered the IL2 molecule and IL2 receptors 20 years ago, and since then, his team has pioneered studies that have determined how IL2 functions as a growth factor for T lymphocytes and Natural Killer (NK) cells, the principal cells known to fight viral infections.

In the hopes of using IL2 therapeutically to bolster the immune system, other investigators have administered high doses of IL2 intermittently, usually for only 5 days every 2 months. Two international randomized, controlled phase III trials supported by the Chiron Corporation have been initiated to examine the clinical benefit of IL2 when given in high doses.

Smith's team took a different approach. Based on their studies of the way IL2 interacts with its receptor, they tried to find a way to give IL2 daily for longer time intervals, hoping to stimulate the immune system continuously. The team at Weill Cornell initiated clinical trials in 1994 using IL2 manufactured by the Amgen Corporation (Thousand Oaks, CA). Their initial phase I dose-finding/safety studies in 16 individuals established low doses of IL2 that are safe and non-toxic, even when given daily for several months.

They then extended their experience to 40 individuals with moderate immune system damage in 1996. This research demonstrated that low doses of Amgen IL2 can be given daily for as long as a year, and results in an increase in NK cells, and the accelerated recovery of the numbers of circulating CD4+ T cells, the cells that are infected with HIV.

On the basis of the findings by the Weill Cornell team, in 1998 the Chiron Corporation (Emeryville, CA), which manufactures and markets a recombinant form of IL2, initiated a multicenter randomized controlled study of 115 subjects suffering from a more severe CD4+ T cell immunodeficiency. The results of this study, for which Dr. Smith is the principal investigator, is the first of the two reports to appear in *HIV Clinical Trials*. The results confirmed and extended the earlier experience of the Weill Cornell researchers. When combined with effective antiviral therapy, daily low

doses of IL2 increased the number of circulating NK cells, as shown in the previous Weill Cornell uncontrolled study. The total CD4+ T cell increase of the IL2 treatment group did not reach significance when compared with the control group within the 6-month study period. However, in the IL2 treatment group there was an accelerated return of the number of new, “naï ve” CD4+ T cells, which are important for rebuilding the immune system. In addition, IL2 treatment lowered the levels of cholesterol and low-density lipoproteins in the blood, a result that was unexpected. Although local reactions at the injection sites occurred, severe systemic side effects were much less frequent than observed in previous trials that employed higher doses of IL2.

The second report details new studies initiated at Weill Cornell in 1999 to determine the effect of discontinuation of antiviral therapy in individuals who continued to receive daily low dose IL2. Individuals were selected who had recovered normal concentrations of circulating CD4+ T cells and had achieved elevated levels of both killer T cells and NK cells. To date, 30 subjects have entered the study, and 9 subjects have undergone one interruption of antiviral therapy, while four subjects have undergone two interruptions. Although all subjects have sustained a viral relapse, the level of virus in the blood appears to have been controlled by killer T cells. After an initial rapid increase in virus, the level of virus in the blood declined by an average of 10-fold, and came to a lower, steady level. Coincident with the decline in viral levels, there was a marked increase in the number of killer T cells in the blood.

Most important, subsequent to the second interruption of antiviral therapy, three of four subjects controlled the peak plasma virus to > 10-fold lower levels compared with the first interruption of therapy, suggesting that the first interruption of therapy contributed to better control of the virus.

These results were unexpected, in that prior studies had shown that chronic HIV infection leads to irreparable immune system damage. This has led some researchers to recommend early diagnosis and treatment of HIV infection. However, these new results indicate that even if HIV infection has been present for several years, after treatment with effective antiviral drugs and IL2, the immune system can recover to mount significant antiviral control.

Accordingly, the way is now open to additional studies to determine how best to augment antiviral reactivity in these individuals. A new, randomized, controlled trial testing therapeutic HIV vaccines in combination with low dose daily IL2 is about to begin at Weill Cornell. In this new trial, the changes in virus and lymphocyte levels that occur after the interruption of antiviral therapy will be monitored as described in the current report to determine the efficacies of the different immunotherapies. This promises to be a rapid and sensitive way to determine the magnitude of the host antiviral response in the whole body; a clinical method that does not rely solely on laboratory assays.

In this way, future phase II clinical trials testing immunotherapies can be conducted with small numbers of subjects (i.e. ~ 100) over short time intervals (i.e. months vs. years). This approach may make it possible to decrease the time for the identification of promising vaccines and immunotherapies to years rather than decades, prior to initiating large phase III therapeutic trials and large prophylactic vaccine trials.

(More)

Other centers involved in the recent studies include Quest Clinical Research, San Francisco, CA; Associates in Medical and Mental Health, Tulsa, OK; Tower Infectious Diseases Medical Associates, Los Angeles, CA; Community Research Initiative, Brookline, MA; Comprehensive Care Center, Nashville, TN; Infectious Diseases Physicians, Annandale, VA; University of Texas Southwest Medical Center, Dallas, TX; Southhampton Medical Group, Houston TX; Central Florida Research Initiative, Almonte Springs, FL; Mercy Hospital, Miami, FL; and Northwestern University, Chicago, IL.

These studies were funded, in part, by grants from the National Institute of Allergy and Infectious Diseases (NIAID) to Dr. Smith, and from the National Institutes of Health (NIH) to New York Weill Cornell's General Clinical Research Center.

#

