

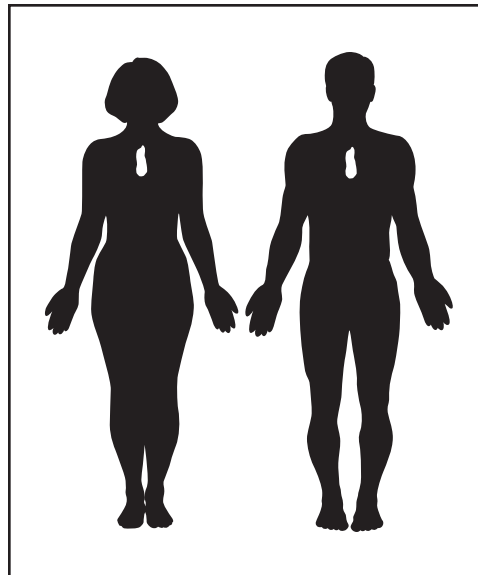
HUMAN GROWTH HORMONE FOR THYMUS RECONSTITUTION

PUBLISHED BY



MARCH 2007

AREA OF STUDY:
the thymus



Interest in using human growth hormone (rHGH, Serostim) to treat various conditions in HIV disease has been piqued for more than a decade. It is approved for treating wasting syndrome in HIV disease. The results from the studies using rHGH to treat body changes (lipodystrophy) have been encouraging, notably for central obesity around the stomach. Its approval for this use is imminent. (For more information on managing unwanted weight loss or lipodystrophy, read Project Inform's publications, *Nutrition and Weight Maintenance* or *Lipodystrophy Syndrome(s)*.)

Several researchers have proposed that rHGH may bolster the immune system in ways that might

improve outcomes in HIV. One theory is that rHGH may stimulate renewal of an important organ in the immune system, the thymus. This may, in turn, lead to improved immune health in people with HIV. Studies are now examining whether or not renewing thymus tissue leads to better health and longer survival.

The thymus is necessary for developing new T cells, like CD4+ and CD8+ cells. Without some thymus present, immune reconstitution that produces a wide range of functional CD4+ cells is not believed to be possible. Thus, the state of the thymus in HIV disease and how therapies affect it are of great interest to those researching ways to restore the immune system.

Napolitano: The first observation

Dr. Napolitano and colleagues from the Gladstone Institute of Human Virology in San Francisco has published striking data using rHGH and its impact on the thymus in people with HIV. The study used rHGH to treat lipodystrophy. The volunteers took doses ranging from 1.5–3.0mg a day for 6–12 months. In a sub-study, a type of x-ray called a CT scan was taken of the thymus on five of them before, during and after using rHGH. All had been on stable anti-HIV therapy for 1–4 years. All had very low HIV levels in their blood, most below the limit of detection of viral load tests. People were relatively healthy, with an average CD4+ cell count about 419.

At six months, marked increases in thymus mass were noted, beyond what has been seen using anti-HIV therapy alone. This increase sustained during the course of rHGH therapy and correlated with more naïve T cells, most notably naïve CD4+ cells. This result suggested that the thymus is functioning properly and helping make new T cells. The development of new, naïve T cells is critical to true immune restoration. When rHGH was stopped, there was a loss of thymus mass. However, CD4+ cell count increases seen over the course of therapy were sustained despite this loss of mass.

While these data are encouraging, researchers have not concluded that the broad and general use of rHGH be recommended for immune restoration therapy. Two of the five volunteers stopped the rHGH due to its side effects. Of note, rHGH can cause joint pain (*arthralgia*) and glucose intolerance, increasing the risk for diabetes.

Another interesting observation

Another study evaluated the immune responses in 12 people with lipodystrophy. They were given 4mg rHGH daily for 12 weeks, along with anti-HIV therapy. They then received placebo, rHGH every other day, or rHGH twice a week for another 12 weeks. Volunteers were then given no rHGH therapy for another 24 weeks. The responses from HIV-specific CD4+ and CD8+ cells were evaluated before, during and after therapy.

After the first 12 weeks, 9 out of 12 volunteers showed marked improvements in their HIV-specific CD4+ and CD8+ cells. Unfortunately, they did not relate to higher overall CD4+ or CD8+ cell counts or lower HIV levels.

Improved HIV-specific CD4+ cell responses were lost by week 24, regardless of whether a person stayed on rHGH or took placebo. Improved HIV-specific CD8+ cell responses were sustained in all groups (including placebo) for the second 12 weeks. By the end of the 48 weeks, HIV-specific CD8+ cell responses waned and HIV-specific CD4+ cell responses remained undetectable.

Herpes-specific CD4+ cell responses were present at study entry and they improved over the first 12 weeks of rHGH therapy. During the second 12 weeks, these responses fell to below pre-study levels. The loss of these responses related to volunteers showing symptoms of herpes.

Investigators conclude that 4mg rHGH a day may be able to improve both HIV-specific CD4+ and CD8+ cell function. The effect on CD4+ cell function does not appear to be sustained with lower doses or when rHGH is stopped.

Herpes-specific immune responses also improved over the first 12 weeks and lost thereafter. While rHGH may bolster immune responses in the short-term, during higher dose daily therapy it might also correlate with a longer-term loss of these functions. The herpes-specific responses were actually higher before starting rHGH than at the end of weeks 24 and 48. This gives reason for caution about using rHGH for immune reconstitution outside studies. While there's interesting and compelling information coming out about rHGH, much more work is needed to define its true risks and benefits.

These early results have led to two larger studies, one conducted by Dr. Napolitano with 20 volunteers and another sponsored by the AIDS Clinical Trials Group (ACTG), which involved 60. Data from both studies were presented at the 2005 International AIDS Society meeting in Rio de Janeiro.

Napolitano: A twenty-person study

During its first six months, Dr. Napolitano's study used of 3 mg rHGH a day injected under the skin (subcutaneous injection). This was followed by 1.5mg rHGH a day for another six months, for a total of one year of daily therapy. To be eligible, volunteers had to have CD4+ cell counts under 400, HIV levels below 1,000 and have been on stable anti-HIV therapy for at least one year. Because

of potential harmful effects of rHGH, people with the following conditions were excluded: diabetes, abnormal glucose tolerance tests, neoplasia, carpal tunnel syndrome, pancreatitis and active cardiac disease. Also, because part of the study's goal was to assess the impact of rHGH on the size and function of the thymus, anyone with an "abundant" thymus was excluded. (This is where a thymus score is greater than or equal to 3.)

The study had a cross-over design. Of the 20 volunteers (all of whom stayed on anti-HIV therapy during the study), 10 took one year of rHGH according to the schedule described above while the other ten were merely observed. After one year, the group on rHGH stopped therapy and was observed for a second year, while the group who hadn't taken rHGH therapy then started one year of it.

Thymic scores that indicate thymic size increased among those on rHGH during the first year, but not among the second group. The average thymus score upon entering the study was 1. (On a scale of 1 to 5, 1 is minimal, barely recognizable while 5 represents a thymus mass the size associated with a cancer, perhaps.) Those on rHGH saw their scores increase by 1.5, while those only on anti-HIV therapy saw slight decreases in their scores, overall, by .02.

Also, these increases in thymus scores (together with increases in measures of both thymus density and volume) related to marked increases in naïve CD4+ cells (69% increase among those taking rHGH during the first year compared to only 9% increase for those only on anti-HIV therapy), but not naïve CD8+ cells. This was further associated with more pronounced increases in total CD4+ cell counts (19% increase among those on rHGH vs. 1% increase among those only on anti-HIV therapy).

Interestingly the most pronounced increase in both naïve and total CD4+ cell counts were seen among those on rHGH with a rise in another natural occurring immune chemical called IGF-1 (insulin growth factor-1). Among those with pronounced increase (more than 3-fold) in IGF-1 levels due to rHGH use, naïve cells increased by 95% and total CD4+ cell counts increased 25%.

Side effects in this study were not insignificant. Among those taking rHGH, side effects included carpal tunnel symptoms (5), edema (2), diabetes (1) and several elevated lab markers including glucose, amylase and triglycerides.

AIDS Clinical Trials Group (ACTG 5174): A sixty-person study

The ACTG conducted a larger 60-person study to follow up on the earlier findings from ACTG 5174. This study included people with CD4+ cell counts under 350 and HIV levels below 400 who had been on stable anti-HIV therapy for at least one year. The 60 people were divided into two groups. One group was given anti-HIV therapy and 1.5mg rHGH a day by subcutaneous injection for 48 weeks. The second group took anti-HIV therapy alone for 24 weeks, followed by 3mg rHGH a day for 24 weeks.

During the first 24 weeks, the first group showed trends toward increases in both naïve CD4+ cells and total CD4+ cells. The second group showed no change in these counts. By the end of 48 weeks, both groups showed notable increases in naïve and total CD4+ cell counts. While the first group took rHGH for a longer period of time, they were on a lower dose that took longer to result in CD4+ cell increases. However, people in the lower dose group showed more pronounced increase (1 log vs. ½ log) by week 48 in another measure of recent thymic activity called TREC (T cell receptor excision circles).

In this study, CT scans were done on a subset of people in each group. Of the 11 people in the lower dose rHGH group who had scans, seven (64%) showed increased thymus mass after 24 weeks while 78% (seven of nine) showed the same effect after 24 weeks on the higher dose.



For more
treatment
information, call
Project Inform's
toll-free
National
HIV/AIDS
Treatment
Hotline at
1-800-822-7422.

Commentary

In all of these studies, using rHGH related to increases in thymus size and naïve and total CD4+ T cell counts. Taken together these studies are promising, but they are not studies of effectiveness. Many questions remain unanswered about using rHGH to treat immune suppression in HIV disease.

Certainly rHGH has shown benefit in treating wasting syndrome in HIV disease and its approval for treating body lipodystrophy is soon likely. It's important that larger studies confirm these early findings. They can tell us whether or not increases in thymus size and naïve and total CD4+ cell numbers, associated with rHGH use, ultimately benefit people living with HIV and result in better quality of life and longer life.

It's unknown, for example, if the increase in CD4+ cells induced through rHGH use are functional. At least the one study looking at herpes responses showed that

while these responses appeared to be bolstered by rHGH in the short-term, when the rHGH was stopped, the responses fell below what they had been before therapy. This related to more herpes outbreaks and disease. Moreover, side effects of rHGH, like diabetes in particular, may make long-term use of the therapy impractical.

Investigators caution against using over-the-counter or internet products that claim to contain human growth hormone. Some of them claim to contain plant-derived growth hormone, others claim to contain cow or goat growth hormone, and still others claim to contain substances that increase the body's production of GH. There is no evidence that any of these products contain either a relevant product or a dose needed to induce the types of effects seen in the study. Over-the-counter and internet sales of these "growth hormone" products are a major source of health fraud.

www.projectinform.org



Go online around the clock and get connected to treatment information in the privacy of your own home!