

The Many Faces of Human Growth Hormone

The story of human growth hormone (hGH) is colorful by drug industry standards. HGH, also known as somatotropin, was first used to treat stunted growth in children. Later it was used in people with HIV disease to treat the gauntness of AIDS-related wasting and, more recently, the fat accumulations associated with lipodystrophy. HGH also may play a role in immune reconstitution. Outside the field of HIV, this very expensive therapy has multiple indications. Unapproved uses for hGH run the gamut from muscle enhancer to purported cure-all. Not surprisingly, the man-made hormone does not always perform as desired. Yet new research into how hGH may fit into the future of HIV disease management warrants another look at this unusual drug.

Bob Roehr

History

Growth hormone is a protein produced by the pituitary gland, a small peanut-shaped “master gland” located at the base of the brain. The pituitary gland not only controls physical growth, but also regulates other glands throughout the body that produce hormones such as testosterone and estrogen.

Scientists first began to learn the secrets of growth hormone by studying and treating children who did not grow normally. Researchers found that injecting ground-up pituitary glands taken from cadavers into the children led to their normal growth and development. The process was limited by

the supply of pituitary glands, and the procedure carried a risk of transmitting slowly developing viral infections such as Creutzfeldt-Jakob disease, a variant of which is popularly known as “mad cow disease.” Ongoing therapy required the harvesting and pooling of glands from large numbers of cadavers.

The solution was genetic engineering, which became a cornerstone for the creation of the modern biotechnology industry. For hGH, the process involves inserting a gene into laboratory cell lines to produce the desired protein, growing huge numbers of these cells, then purifying out the protein they produce for subsequent human use. The insertion of

genes into cells is known as recombinant gene technology. The first version of recombinant human growth hormone (sometimes called rhGH) was made by Genentech of South San Francisco, California, and approved for sale by the U.S. Food and Drug Administration (FDA) in October 1985. Today several companies produce and market recombinant hGH under different brand names (see sidebar on this page).

Recombinant technology solved the problems of disease transmission and availability, but not of cost. hGH is extremely expensive—from several thousand dollars per year for limited supplemental use, to about \$35,000 per year for a child who completely lacks the protein. The huge cost (and profit) of making the complex molecule has encouraged manufacturers to find other uses for hGH beyond the initial indication for children with stunted growth.

Pituitary tumors, chronic illness, side effects of therapy for other medical conditions, and processes associated with aging all can contribute to reduced pituitary function and decreased production of growth hormone. Expansion of the hGH market to treat such conditions was a natural outcome, and the FDA has approved label indications for new uses as manufacturers have submitted evidence of success from clinical trials.

At the same time, some proponents of hGH paint a dazzling but false portrait of the substance. Many sites on the Internet tout hGH as a panacea for everything from losing weight to halting the aging process. Some bodybuilders use growth hormone, often illegally, to rapidly increase muscle mass. Claims have proliferated though evidence to support them is scant. Growth hormone can be very beneficial for correcting a deficiency, but having too much of it does not necessarily bring added benefit—though it does increase the risk of side effects. Nevertheless, illicit use of hGH appears to be widespread.

AIDS Wasting

AIDS wasting syndrome (cachexia) is a condition associated with advanced HIV disease. It involves overall weight loss, but more importantly, the loss of lean body mass, or muscle, which sometimes may be replaced by fat. Weight loss results from a number of factors, alone or in combination, including lack of appetite, nausea, diarrhea, oral problems that make eating difficult, and problems related to intestinal absorption and use of nutrients. The condition was much more prevalent in the developed world before combination antiretroviral therapy became available.

A correct diagnosis and the proper intervention for each individual are as important in treating AIDS wasting as they are for any other medical problem. Early intervention is often most successful, and a variety of effective and relatively inexpensive tools (such as nutritional supplements, appetite stimulants, and exercise) can be used. hGH is not a universal remedy for treating AIDS wasting. While it can have a dramatically beneficial effect in some individuals (presumably those with a deficiency of natural hGH), the majority may see no benefit.

HGH by Other Names

hGH (somatropin) is produced by several companies and sold under a number of brand names. The main distinction between them is that they are produced in different types of cell lines and have been evaluated in clinical trials for different indications. The FDA allows a company to claim a label indication only if it has conducted trials for a specific condition with that version of hGH. Most physicians, however, believe that the different versions of hGH have the same biological effects. The most common brands of hGH sold in the U.S. are:

Genotropin and Genotropin MiniQuick
manufactured by Pharmacia (Pfizer)

Humatrope
manufactured by Eli Lilly and Company

Norditropin
manufactured by NovoNordisk

Nutropin and Nutropin AQ
manufactured by Genentech

Protropin
manufactured by Genentech

Saizen
manufactured by Serono

Serostim
manufactured by Serono

The current hGH regimen for AIDS wasting consists of a daily injection administered at bedtime to mimic the natural cycle of growth hormone release into the bloodstream. The dose is 4–6 mg, based upon body weight. hGH alone is likely to result in weight gain that is primarily fat, while adding a regimen of resistance exercise, such as weight training, can help build lean body mass. The average cost of hGH therapy for AIDS wasting is approximately \$250 per day. Due to pressure from AIDS activists, Serono Laboratories, which produces a version of hGH known as Serostim, capped the cost of their hGH at \$36,000 per calendar year for qualified individuals. The company provides the drug free of charge beyond this point.

Lipodystrophy

The term “lipodystrophy” is broadly applied to issues of body fat irregularities and metabolic abnormalities associated with HIV disease. It can include the wasting of fat from the face, arms, legs, and buttocks, as well as an increase in fat around the abdomen and on the upper back. Metabolic

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Graeme Moyle, MD

abnormalities include increased blood lipid (fat) levels and insulin resistance (inability of cells to properly use insulin, leading to blood sugar imbalances). There is little agreement on a measurable definition of lipodystrophy, which impedes research into the condition.

Consensus appears to have emerged, however, around the idea that there are likely several different biological mechanisms and various factors at play, either alone or in combination. Some of the manifestations of lipodystrophy may be associated with HIV infection itself, others with specific anti-HIV drugs, and still others with the natural processes of aging. The picture is further complicated by individual genetic factors, body chemistry, and lifestyle choices.

Successful strategies to treat the various manifestations of the syndrome have not been identified. “In broad terms, management approaches to lipodystrophy tend to be dictated by ‘fashion’ and perhaps ‘marketing’ rather than fact or science,” writes Graeme Moyle, MD, of London’s Chelsea and Westminster Hospital in the most recent *Medscape* treatise on the subject. Researchers are gathering scientific data to investigate the use of hGH for some symptoms of lipodystrophy—however curious it may seem to reverse increases in abdominal fat, for instance, with a drug that can promote fat gains in people with wasting.

Donald Kotler, MD, of St. Luke’s-Roosevelt Hospital in New York City is the principal investigator of the most sophisticated study of hGH and lipodystrophy yet conducted. The trial is known as STARS—Serostim in the Treatment of Adipose Redistribution Syndrome (ARS is another proposed term for lipodystrophy). In late September Dr. Kotler presented the most recent results from the study at the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Diego.

The multicenter STARS trial randomized 239 HIV positive subjects (13% female, 20% non-Caucasian) with an abnormal waist circumference or waist-to-hip ratio (waist circumference divided by hip circumference) to take 4 mg hGH daily, 4 mg hGH every other day, or placebo for 12 weeks. Participants then entered a second 12-week phase during which those who had received daily hGH were randomized to receive placebo (27 subjects) or hGH on alternate days (23 subjects); those who began taking hGH on alternate days continued to do so (48 subjects); and the initial placebo group went on to take 4 mg hGH daily (53

subjects). Everyone received hGH at some point during the 24-week trial, but no one received it on a daily basis for more than half the trial.

Principal measurements for the trial were the reduction of visceral adipose tissue (VAT, which is firm, internal abdominal fat, not the soft fat that lies just beneath the skin); levels of non-HDL (non-high-density lipoprotein) cholesterol; insulin resistance; lean body mass; and self-assessed quality of life and body image. Increased VAT, elevated non-HDL cholesterol, and insulin resistance are risk factors for cardiovascular disease. DEXA scanning technology was used to measure internal VAT. Mean (average) age at baseline was 45; mean body mass index (calculated as weight divided by height squared) was 27 kg/m². Average baseline VAT was 331 cm² in men and 249 cm² in women, which was significantly greater than in healthy control subjects of similar sex and age.

Dr. Kotler’s group found that daily use of hGH was necessary to achieve a statistically significant reduction of visceral fat (at least at the 4 mg dose) in the 151 subjects who completed 24 weeks. Switching to alternate-day use after initial daily use was sufficient to keep internal fat from returning, but if hGH was stopped completely, the fat came back. At 24 weeks, people who received daily hGH then placebo showed a mean reduction in VAT of 22.4 cm²; those who stayed on alternate-day dosing for the full 24 weeks had a mean reduction of 19.7 cm²; those taking placebo followed by daily hGH lost a mean of 30.5 cm²; and subjects who began taking daily hGH and continued on an alternate-day regimen had a mean reduction of 30.9 cm² of VAT. DEXA scanning showed that these reductions were primarily in trunk fat, not in the limbs. For the four groups mentioned above, the VAT fat losses were 1.9, 3.0, 3.5, and 5.0 lbs, respectively. Loss of limb fat was 0.2, 0.4, 1.1, and 1.5 lbs, respectively, with an average loss of about 0.25 lbs per limb.

HGH reduced non-HDL cholesterol levels in all groups, with the decline ranging from 6.6% to 8.4%. The greatest benefit came with daily dosing followed by alternate-day maintenance dosing. Those who were later switched to placebo saw their non-HDL cholesterol levels start to climb again, though levels were still below baseline 12 weeks after stopping the hGH injections.

S **eron Laboratories’ patient assistance program, which provides hGH for AIDS wasting for compassionate use and support above the \$36,000 annual cap, can be contacted at 888-628-6673.**

With regard to insulin resistance, the three arms of the trial that started on hGH showed an identical pattern of an increase in mean area under the curve (AUC) serum insulin through week 12, then a significant decline toward baseline by week 24. (AUC here refers to total insulin concentration over a period of time.) The arm that started on placebo showed no increase until hGH was initiated; this group was not tracked long enough to note a decline. However, AUC insulin levels tend to correlate poorly with true measures of insulin sensitivity.

Dr. Kotler concluded that the reduction of VAT, the decrease in total and non-HDL cholesterol levels, and the return of insulin levels to baseline by the end of the study suggest that hGH therapy could lead to a reduction of cardiovascular disease risk in this population. Nevertheless, it is important to remember that these results are from limited clinical trials. No version of hGH is approved by the FDA for treatment of lipodystrophy. While physicians have the flexibility to prescribe off-label (unapproved) use of hGH, health insurance providers most often will pay for only label-indicated uses of a drug, and few people can afford to pay for hGH out of their own pockets.

Thymic Function

New evidence suggests that hGH also may enhance immune system restoration and HIV-specific T cell responses. At the XIV International AIDS Conference in Barcelona, Spain, this past summer, researchers from Chelsea and Westminster Hospital presented data showing a direct effect of hGH on thymic function in a very small group of people with chronic HIV infection taking antiretroviral therapy. The thymus, a lymphoid organ located behind the upper breastbone, is the site of T cell maturation and differentiation—that is, where these white blood cells learn to recognize antigens (substances that stimulate an immune system response).

After 12 weeks of hGH administration (4 mg per day), 11 of 12 subjects in this study showed significant increases in naive CD4 and CD8 cell counts, indicating boosted thymic activity. Naive T cells are necessary for immune reconstitution, as memory T cells are programmed to target previously encountered antigens and do not respond to new pathogens introduced into the body (for example, those causing certain opportunistic illnesses, or OIs). In addition, HIV-specific memory CD4 and CD8 responses were significantly improved in at least nine of the 12 subjects after 12 weeks of hGH therapy. The memory CD4 response, however, was sustained only in those who continued taking daily hGH (instead of alternate-day or twice-weekly dosing) through week 24.

While these recent data are intriguing, much more study is needed. Even if it proves viable, clinical use of this potential new indication for hGH is likely years away.

Risks and Side Effects

Because hGH is a protein that would be destroyed in the stomach and intestines by digestive enzymes, it cannot be

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taken as a pill and must be injected subcutaneously (under the skin).

HGH should not be taken by people with acute critical illness due to complications of open heart or abdominal surgery, multiple accidental trauma, or acute respiratory failure. HGH may stimulate the growth of active tumors and should not be used by people who have cancers that are not under control. HGH also may affect blood triglyceride levels and may increase the risk of developing diabetes in those who are already at risk, particularly people who are obese. Individuals taking insulin may need to have their doses adjusted. In spite of Dr. Kotler's findings, there may be increased cardiovascular risk with long-term hGH use, perhaps related to insulin resistance. Studies of growth hormone have not been conducted in pregnant women.

Up to 50% of all people experience mild to moderate musculoskeletal discomfort when starting hGH, and about 25% experience some fluid retention and swelling of the hands and feet. While both generally decrease as the body becomes accustomed to the drug, a significant number of people must stop taking hGH due to these side effects. Some people develop carpal tunnel syndrome (CTS, a condition characterized by numbness, pain, or tingling in the wrists or hands) while taking hGH; CTS typically resolves when the drug is discontinued. Other possible side effects include nausea, diarrhea, flu-like symptoms, and chest pain; only rarely are these severe enough to require discontinuation of treatment.

Dollars and Fraud

The high price tag and potential off-label and illegal uses of hGH appear to be strong incentives for criminal activity by corporations and individuals alike. Genentech illegally promoted off-label use of hGH in the first decade after it was approved. The FDA sued, and in 1994 the company agreed to pay a \$50 million fine for the violations.

In late 2001 Phoenix, Arizona, witnessed a complex web of false drug orders, a bungled hijacking, theft, arson, insurance fraud, and murder over a shipment of hGH. A wholesale value of about \$1 million and a street value three times that amount set these events in motion.

Counterfeiting of hGH is a growing problem. Like sidewalk vendors selling \$20 Rolex watches, Internet sites offer

cut-rate growth hormone prices that often are too good to be believed—and should not be. But counterfeit drugs can also enter the regular distribution chain, complete with knock-off packaging and bogus manufacturing lot numbers. In January and May 2001, and again in May 2002, Serono and the FDA warned about circulation of counterfeit Serostim distinguishable only by small variations in lot number and package design. Some of the counterfeits have little or none of the claimed active ingredient and they may contain dangerous impurities.

Serono—though apparently no other manufacturer of hGH—considers the problem so significant that it established the Serostim Secured Distribution Program. As of November 1, 2002, the distribution network has been restricted, and every single dose of Serostim has a number and is tracked directly to the patient. This helps to assure the quality of the drug. It also minimizes the likelihood of drugs being diverted and reduces the potential for reimbursement fraud.

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Is Your Health Going Up In Smoke?

Smoking is a habit. It is often a stress-related activity. Smoking is also a risk factor for many diseases that affect people with HIV, including cardiovascular disease, bone disease, and anal cancer.

The FDA has approved bupropion (Zyban) as a nicotine-free medicinal quitting aid. Nicotine replacement therapies—in the form of lozenges (Commit), patches (Habitrol, NicoDerm CQ, Nicotrol), inhalers (Nicotrol Inhaler), and gum (Nicorette)—are another means of quitting. Complementary methods include behavior modification, counseling, and support.

The Stop Smoking Center (www.stopsmokingcenter.net) is a unique web site that offers a Quit Program, online support services, and links to a wide range of smoking cessation resources, including the American Lung Association (212-315-8700) and Nicotine Anonymous (415-750-0328).

The Tobacco Education Center of UCSF/Mt. Zion (415-885-7895) is a quitting resource for San Francisco Bay Area residents.

Learn more about the art of quitting. There is no better time than now.