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The Use of Human Growth Hormone for Children with Idiopathic Short Stature

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Executive Summary

Inadequate production of growth hormone (GH) results in short stature, defined as a height for a given age that is two or more standard deviations below normal. Children with short stature may have classic GH deficiency or an underproduction or insensitivity to normal levels of GH caused by pathologies such as Turner's syndrome or renal insufficiency. Idiopathic short stature (ISS) results when children are short, compared to others in their age cohort, for unknown or hereditary reasons. There are an estimated one million children with ISS and 24,000 with medically defined short stature in the United States. Recombinant human growth hormone (rhGH) was first produced in 1985 and is now available in potentially unlimited amounts. This report evaluates the use of rhGH for children with ISS.

A paucity of data hampers the evaluation of the use of rhGH for children with ISS. The majority of studies have small sample sizes, a retrospective design, and/or lack a similar, prospective, untreated control group. Published data indicate the use of rhGH can increase linear growth rate and height in children with ISS but its effects on final adult height have not been clearly established. However, it is not clear that final height should remain the predominant criterion for evaluating its effectiveness; the growth induced by rhGH may itself be a benefit if it provides psychological benefits at a time when children are developing their self-image. The vast majority of patients receiving rhGH report no adverse effects. Many of the short-term complications can be easily managed. The long-term safety of rhGH, however, has not yet been determined.

The cost of rhGH varies somewhat (due to differences in dose, frequency): usage usually continues for 4 to 5 years and costs approxiately $20,000 annually.[1] No data currently exist evaluating the cost-effectiveness of rhGH for children with ISS. Most health plans do not cover rhGH for ISS in their policies but have paid for it on a case-by-case basis.

The use of rhGH for children with ISS is controversial. Optimal rhGH regimens, particularly regarding when to initiate or terminate usage, are not clear; patient selection criteria have not been established; and there is no standard or reliable means for identifying GH deficiency. Ethical concerns raise additional controversies, including the appropriateness of using rhGH for children who may not have a "disease" or "disability" and the difficulty of defining and advancing the well-being of children with short stature.

Conclusions

- Growth Hormone therapy is both the standard of practice and FDA approved for children of short stature with classic GH deficiency, chronic renal failure, and Turner's syndrome.
- In comparison, for children with ISS, appropriate patient selection criteria, optimal rhGH regimen, and other treatment variables for rhGH have not yet been established.
- While the use of rhGH for ISS shows little risk of serious short-term harm, the long-term risks are not yet known.
- The benefits of using rhGH for ISS can not yet be determined. While rhGH appears to increase the growth rate of children with ISS, its effect on final adult height is not clear. There is also disagreement as to whether final height or some other criterion, such as accelerated growth, should be used to measure the benefit of the use of rhGH for ISS.
- The use of rhGH for ISS raises a host of controversial and unresolved ethical issues.
- rhGH for ISS is not included in the coverage by many health plans.
- No cost-effectiveness data exist for rhGH for ISS.

Recommendations

- The long-term safety, efficacy, and cost-effectiveness of the use of rhGH for ISS should be established through additional studies.
- At this time, rhGH should be used for ISS only in controlled settings that generate data on the intervention's safety and efficacy.
- Individuals responsible for determining the benefits set for public or private insurance products should carefully weigh the value of the use of rhGH for ISS as safety and efficacy data evolve.
- Health professionals should help parents and children address the problems that stem from ISS.

Background

Endogenous growth hormone modulates lipid, carbohydrate, and protein metabolism, fluid balance, and stimulates the development of bone, cartilage, skeletal muscle, and gonadal tissue. These processes together are responsible for longitudinal growth. Inadequate production of GH results in short stature, defined as a height for a given age that is two or more standard deviations below normal.[2,3] Underproduction or insensitivity to normal levels of GH can be caused by pathologies such as Turner's syndrome, Prader-Willi syndrome, Noonan's syndrome, renal insufficiency, Down's syndrome, juvenile chronic arthritis, spina bifida, or intrauterine growth. Idiopathic short stature (ISS) results when children are short, compared to others in their age cohort, for unknown or hereditary reasons.[4] ISS has recently been subdivided into (a) familial short stature, characterized by short parents and no bone age delay; (b)

constitutional delay, characterized by bone age delay and late onset of puberty; (c) a combination of familial short stature and constitutional delay (e.g., short parents and late onset puberty with or without bone age delay); and (d) an unclassifiable subgroup. Advances in molecular biology have allowed for the production of pure recombinant human growth hormone (rhGH) for treatment of children with all short-stature indications.

There are an estimated 1,062,000 children with ISS and 24,000 with medically defined short stature between the ages of 4 and 15 in the United States.[5] Minnesota's 1997 population was 1.75% of the total United States population, and therefore there are approximately 18,600 children with ISS and 420 children with medically defined short stature between the ages of 4 and 15 in Minnesota. The total number of children ages 4-15 in Minnesota who may seek rhGH therapy is therefore estimated at 19,000. Genentech reports that there are approxiately 324 active non-ISS patients and 55 ISS patients on rhGH in Minnesota. These represent numbers from June 30, 1997 to November 30, 1999 and includes all patients for whom no discontinuance of treatment form has been received. Genentech also estimates that they represent 80% of the market for rhGH in Minnesota. These numbers were obtained from Genentech and the National Cooperative Growth Study.

Endogenous human growth hormone

Endogenous human growth hormone (GH), or somatropin, is a polypeptide secreted by the pituitary gland. Once in the bloodstream, GH interacts with either a phosphate group or a combination of phospholipid breakdown products and protein kinase C, initiating a metabolic cascade that exerts direct effects on peripheral tissues and activates the production of insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3). When bound to IGFBP-3, IGF-I augments the direct effects of GH and mediates other processes. Alone or with IGF-I, GH stimulates tissue differentiation, cell proliferation, protein synthesis, and lipolysis; modulates lipid, carbohydrate, and protein metabolism, fluid homeostasis, and fluid-electrolyte balance; regulates the expression of numerous hepatic proteins, including lipoproteins; influences the differentiation of adipose tissue, the development of gonads, and the proliferation of bone marrow and peripheral macrophages and lymphocytes; and stimulates the development of bone, cartilage, and skeletal muscle tissue, and longitudinal growth.[6,7]

Two proteins controlled by the hypothalamus, GH releasing hormone (GHRH) and somatostatin, respectively activate and suppress the synthesis and release of GH. However, the secretion or action of GH is influenced by numerous factors. IGF-I itself feeds back on the hypothalamus and pituitary gland to suppress GH release. GH secretion is also suppressed by high blood glucose levels and increased by low blood insulin levels and high levels of gonadal steroids, particularly testosterone and estrogen. Further, the response of GH to GHRH is decreased in the presence of low counts of certain neurotransmitters (e.g., dopamine agonists, alpha adrenergic agonists, serotonin). In conditions for which nutrient levels are low or catabolic rate and secretion of cortisol and catecholamines are high, serum levels of IGFBP-3 and/or IGF-I are low despite increased GH levels, suggesting resistance to the action of GH. Finally, any genetic defect, disease, injury, surgery, irradiation, or drug therapy that affects the hypothalamus or pituitary may result in decreased production or release of GH as well as other pituitary-derived hormones.[6,8]

In children and adolescents, the rate of growth in height is primarily determined by

the rate at which endogenous GH is secreted. The growth spurt during puberty is caused by increased secretion of GH, secondary to increased secretion of gonadal steroids. Under normal conditions, both GH secretion and growth rate remain increased until the first appearance of menses in girls or thicker facial hair in boys and begin to decline during the development of full pubic hair until final height is reached, after which GH secretion is reduced to a steady state.

Recombinant human growth hormone

In 1985, scientists were able to produce human growth hormone from a genetically altered bacterium (*Escherichia coli*). In October of the same year, the FDA approved the new drug, named Protropin, for use in treating children with growth hormone deficiency or chronic renal failure. In December of 1996, recombinant growth hormone was approved for use in treating girls with Turner's syndrome. Although physicians and scientists had been using natural growth hormone derived from the pancreas of cadavers since 1958, the advent of recombinant human growth hormone has allowed for an essentially unlimited supply of the drug.

Recombinant GH is available in two forms, somatropin and somatrem, which both consist of a sequence of 191 amino acids that is identical to that of endogenous, pituitary-derived human growth hormone, also known as somatropin. The only difference between the two recombinant forms is that somatrem has an additional amino acid, methionine, on the N-terminus of the molecule. Numerous rhGH products are available commercially. Treatment typically consists of 3 to 7 self-administered subcutaneous (SC) or intramuscular (IM) injections of rhGH per week at doses that depend on the condition being treated, the patient's weight and height, the type and severity of side effects, and the degree to which GH-regulated proteins or enzymes, such as IGF-I, are normalized. Thus, the administration schedule and dose must be individualized for each patient. Treatment may continue until attainment of a particular target height or until no further growth is expected based on a slow rate of linear growth (< 1 to 2 cm/year) or on fusion of the articulated ends of long bones, the epiphyses.[9,10] Based on extensive study and FDA-approval, rhGH treatment may be considered standard practice for increasing height in children with GH deficiency, chronic renal insufficiency, or Turner's syndrome.

Evaluation of Evidence

Statistical Issues and Study Design

While data on GH treatment in children is extensive, the majority of studies reviewed herein are hampered by retrospective design, small sample size, and/or lack of a similar, prospective, untreated control group. In most of these studies, randomization is lacking and is used primarily for assessing different doses of rhGH, rather than for comparing rhGH with placebo or no treatment. Another prevalent flaw in these studies is the use of historical controls and/or projected height methodology based on data from historic controls. Since average heights of many specific populations tend to increase over time, primarily due to improved medical care and nutrition, current populations may be taller than their historic counterparts without any specific intervention for growth. Use of historical data may lead to overestimation of rhGH treatment effects by an average of 30%, with growth resulting from other changes being attributed to rhGH.[11]

Further, while national and international growth study databases provide large patient samples from which to derive information about the effects of rhGH, centers reporting to these databases have differing methods of collecting data and do not all report on the same growth parameters. Thus, for any specific patient sample derived from such a database, reported mean values for any growth parameter include only the subjects for which that information was available, rather than all study subjects.[12] A similar phenomenon was observed in several center-specific studies that involved increasingly smaller study samples over the course of the study to the point that 3-or 4-year results may only involve a few subjects.

Additional problems in these studies make it difficult to adequately evaluate the efficacy of rhGH. These include differences in criteria for diagnosing GH deficiency and for defining final height; differences in rhGH dose, frequency, and duration, even in similar patient subgroups; failure to control for puberty and adequately compare the effect of puberty with and without rhGH; and, frequently, failure to control for the effects of steroids, hormones, or other therapy used concurrently with rhGH. Finally, due to the high cost of rhGH, several studies reviewed herein received rhGH products and/or partial or full study funding from rhGH manufacturers. While there is no apparent bias in these studies, the potential for bias exists and results from such studies must be viewed with this in mind.

Efficacy

Data suggest that rhGH can be effective in increasing linear growth rate and height in children of short stature, regardless of the cause of growth failure. However, the effects of rhGH on final adult height are not clearly established due to lack of data, inconsistent data, limitations in study design, and differences in methods for determining final height.

Details from studies assessing the effects of the use of rhGH in children with ISS are provided in Appendix 2. Growth hormone therapy increases growth rate and height and may minimally increase final height, as compared with baseline predicted values. Generally it does not increase final height to normal levels, likely due to rhGH-induced advancement and shortening of puberty in this population. The administration of rhGH in these ISS children promotes a significant increase in linear growth for up to 4 years of therapy, as compared with values at baseline or in untreated controls. While improvement in growth rate followed a similar pattern as that observed in children with classic GH deficiency (nearly doubling after the first year and declining thereafter), overall improvement in growth was somewhat lower.[13, 14, 15, 16] Doses of 31.5 IU/m^2/week or higher appear to be more effective in inducing short-term growth.[13. 17]

Findings were inconsistent with respect to rhGH effects on final height in children with ISS. The two largest studies providing these data[18,19] showed that the use of rhGH for ISS may increase final height, as compared with initial predicted values or untreated ISS subjects, although the increase is minimal and final height is still lower than that in the normal population. Conversely, three smaller studies[15,14, 20] showed no improvement or a loss in final height over initial predicted values or untreated controls. The Wit et al. (1995) and Kawai et al. (1997) groups observed earlier and shortened puberty in rhGH-treated subjects, as compared with controls, and suggested that these GH effects on puberty may be responsible for the disappointing results. Kawai et al. (1997) explain that, in children with ISS, changes in height in

relation to bone age can be divided into three stages: stage 1 occurring before 8 years bone age, stage 2 occurring between 8 and 11 years bone age, and stage 3 occurring after 11 years bone age (puberty). In both treated and untreated children in their study, height gain decreased as bone maturation progressed during stage 1, and height gain remained constant during stage 2. However, during stage 3, while height gain continued at a constant level in untreated children, it gradually decreased in treated children, resulting in a shorter final height than that of the untreated group.

There are wide interindividual variations in response to the use of rhGH in ISS. While numerous variables were identified as predictors of response, these were not consistent among reviewed studies. An analysis of data from the large database of the Kabi Pharmacia International Growth Study[21] revealed the most important predictors of response to rhGH for non-GH-deficient children are the dose of rhGH (positive correlation) and the chronological age of the patient at the time of treatment initiation (negative correlation).

It is not clear whether final height should remain a predominant criterion for evaluating the use of rhGH in children with idiopathic short stature. The growth induced by rhGH may have psychological benefits at a time when children are developing their self-image. A few studies have shown that rhGH may have other benefits, such as improved body fat/muscle composition and protein/lipid metabolism, which contribute to improved overall health and reduce atherosclerotic risk.[13. 58] Further study, however, is required to confirm such rhGH benefits since only a few studies assess these parameters.

Safety

Reported side effects of rhGH include pain (13.6%), rhinitis (11.4%), arthralgia (13.6%), paresthesia (13.6%), development of GH antibodies (2%), mild and transient peripheral edema (2.5%), carpal tunnel syndrome (.2%), benign intracranial hypertension (.2%), carbohydrate intolerance (.4%), pancreatitis, gynecomastia, increased growth of pre-existing birthmarks, pigmentation, exacerbation of pre-existing psoriasis, headache, seizures, injection site burning or pain, weakness, mild hyperglycemia, mild glucosuria, hypoglycemia, hypothyroidism, hematuria, fibrosis, rash, inflammation, bleeding, lipoatrophy, and iron deficiency.[9,22,23,24] While the overall incidence of many of these complications was not reported, the vast majority of subjects treated with rhGH in the reviewed studies experienced no adverse effects and many of the complications can be easily managed. Other reported rhGH effects include an increase in left ventricular mass index[17], an increase in serum lipoprotein (a), and subtle changes in immune parameters[25] although the clinical significance of these effects is not clear. No mortality directly or indirectly associated with GH therapy has been reported in children receiving rhGH.

Safety of long-term rhGH treatment

There are several concerns regarding the potential for deleterious effects with long-term administration of rhGH at the supraphysiological doses used commonly today for most indications. Most troubling is the oncogenic potential of rhGH therapy, particularly in patients already treated successfully for malignancy. This concern is supported by findings from animal and in vitro studies demonstrating that supraphysiologic doses of rhGH induce neoplastic transformation and growth; by the increased incidence of colonic polyps and adenocarcinoma in patients with

acromegaly, a condition involving a sustained high secretion of growth hormone; and by the development of de novo leukemia in 12 Japanese children receiving GH therapy for GH deficiency. While leukemia has developed following GH therapy in several other patients, most American and European patients so affected had risk factors for leukemia, including prior malignancy, treatment with radiation or chemotherapy, or myelodysplasia or disease associated with increased spontaneous chromosomal breakage, such as Fanconi's anemia or Bloom syndrome. However, the development of leukemia in the Japanese cohort remains unexplained since none of the patients had known risk factors for leukemia.[26, 27] An analysis of data from over 12,000 patients receiving rhGH [28] found the incidence of de novo extracranial, nonleukemic neoplasms to be virtually negligible (0.15%) and no greater than that in the general population.

To determine if GH therapy increases the risk for de novo or recurrent malignancy, Ogilvy-Stuart (1995) analyzed data from four early published studies involving GH therapy. Findings revealed that GH therapy did not increase the risk for tumor recurrence, did not increase the risk for de novo leukemia in patients without leukemia risk factors, but did increase the risk for de novo leukemia by 2.5 fold, as compared with the general population, in patients with leukemia risk factors. However, most of the patients in this analysis who underwent GH therapy received much lower rhGH doses than are currently administered.

Though not as yet investigated, another concern is the potential for irreversible joint disturbances following high-dose GH therapy. Between 53% to 76% of the patients with acromegaly develop such problems, including widening of joint spaces, osteophyte formation, joint capsule calcification, mineralization of ligamentous insertions, chondrocyte hypertrophy, and cartiliginous disorganization. These disturbances typically present approximately 10 years after the onset of acromegaly; thus, it is possible that long-term high-dose GH therapy may lead to the subsequent development of similar problems, particularly in patients with pre-existing abnormalities in cartilage or bone growth, such as those with acromegaly or Turner's syndrome.[27]

Cost and Cost-Effectiveness

The average wholesale prices for rhGH products commercially available in the U.S. are as follows :[29]

Humatrope® (somatropin; Eli Lilly and Company): $210.01 for a 5-mg vial; $1260 for a package of six 5-mg vials.

Nutropin® (somatropin, Genentech, Inc.): $420 for a package of two 5-mg vials; $840 for a package of two 10-mg vials.

Nutropin-AQ® (somatropin; Genentech. Inc.): $420 for one 2-mL vial (5 mg/mL); $2520.00 for a package of six 2-mL vials (5 mg/mL).

Protropin® (somatrem, Genentech, Inc.): $420 for a package of two 5-mg vials; $840 for a package of two 10-mg vials.

Genotropin® (somatropin; Pharmacia & Upjohn Co.): $315 for a package of five 1.5-mg vials; $210 for a 5.8-mg vial; $1050 for a package of five 5.8-mg vials.

Norditropin® (somatropin; Novo Nordisk): $168 for a 4-mg vial; $336 for an 8-mg vial.

Serostim® (somatropin; Serono Laboratories): $1470 for a package of seven 5-mg vials; $1764 for a package of seven 6-mg vials.

Based on the cost of one single-use vial of rhGH per day and a dose of 0.3 mg/kg/week in 7 daily doses, the annual cost of treating a child weighing 30 kg is approxiately $20,000.[1] Nevertheless, the cost of rhGH treatment varies considerably due to differences in the dose and frequency of rhGH, which vary with the diagnosis, patient characteristics, and tolerance or danger of adverse reactions in different disease processes. These figures only reflect the cost of the rhGH product and do not include the costs of physician and laboratory fees.

No data currently exist evaluating the cost-effectiveness of rhGH treatment for ISS.

Issues of Controversy

Patient Selection and Diagnosis

No universally accepted patient selection criteria have yet been established and many medical centers determine their own criteria. Likewise, the etiologies of growth retardation and GH deficiency in children with short stature can be confounded by other clinical problems. In 1995, a group of pediatric endocrinologists in Minneapolis/St. Paul, Minnesota developed consensus guidelines for the diagnosis, monitoring, and treatment of children with short stature.[59] See Appendix VI. Regardless of diagnosis, the optimal age for initiation of rhGH therapy has not been determined.

Diagnosis of Endogenous GH Inadequacy

The diagnosis of GH deficiency or neurosecretory dysfunction remains problematic. Serial monitoring of spontaneous GH levels over a 24-hour period is expensive, labor-intensive, and used primarily as a research tool. Diagnostic cut-off values for GH stimulation tests are not standardized and are viewed by many experts as arbitrary. Moreover, there are substantial discrepancies among the findings of different GH assays used to determine GH levels; thus, confirming a diagnosis of inadequate endogenous GH secretion depends on the assay being used. These tests as well as indirect means of determining endogenous GH secretion (measurement of serum IGF-1 and IGFBP-3 or urinary GH) are fraught with questionable specificity, false failure rates, and lack of published age- and sex-specific normal ranges.

Due to the inadequacies of these tests, a subnormal growth velocity often becomes the deciding factor in choosing to initiate GH therapy. However, measurement of short-term growth velocity is unreliable in predicting future growth. Growth velocity during the autumn and winter may be lower than that during the rest of the year by more than 2 cm/year and may be normal even if less than 2.5 cm/year during these cooler seasons. When performed by skilled personnel, the 95% confidence limits for a single height measurement is only +/- 0.5 cm and the confidence interval for yearly measurements ranges from the 8th to the 52nd percentile. Finally, there appears to be no correlation between year-to-year growth velocities over a 2-year period.[27,30,31] The determination of GH levels is extremely difficult given current diagnostic

techniques, making universal recommendations for use problematic.

Optimal rhGH Regimen

While manufacturers clearly identify the recommended starting dose for each FDA-approved use of their rhGH products, doses reported among reviewed studies vary greatly for both approved and nonapproved indications. Doses vary with the rhGH product used as well as the disease process being treated. Since not all researchers identify the rhGH product under investigation and many report dosage by body surface area (m^2) rather than weight (kg), it is difficult to determine whether lower-than recommended dosing induces adequate catch-up growth or higher-than recommended dosing increases the incidence or severity of adverse effects. The frequency of rhGH injections also varies greatly, ranging from 2 to 7 times a week in studies and 3 to 7 times a week in manufacturers' instructions. However, some data indicate that a weekly dose of rhGH divided into daily injections increases growth rate to a better degree than the same weekly dose divided into three injections in patients with GH deficiency and those with Turner's syndrome. In contrast, twice-daily injections appear to be no more effective than once-daily injections. Some data also suggest that evening injection produces hormone and metabolite patterns that are significantly closer to normal than those achieved with morning injection.[9,32,33,34]

Regardless of diagnosis, the optimal age for initiation of rhGH therapy has not been determined. Much data indicate that rhGH should begin as early as possible following diagnosis of a height deficit or a disorder known to be associated with a height deficit. Several groups have found greater benefits with rhGH before rather than during or after puberty and have recommended initiating rhGH several years before puberty; however, the actual pubertal rhGH benefit is difficult to assess if there has been no control for gender growth differences and spontaneous versus steroid-induced puberty.[35,36,37,38]

When to discontinue rhGH is also not resolved. Researchers variously report ending therapy when the epiphyses have fused, when growth rate decreases to 2.5 cm/year, when bone age suggests no further height potential, or when patients reach the 50th percentile for target height, fall within the 3rd to 10th percentile for normal height, or achieve a height consistent with midparental height. These can range from the ages of 13 to 23 for different individuals. It is important to stop rhGH as soon as possible to prevent side effects, minimize cost, and avoid disappointed expectations as length of dose is not necessarily directly related to increase in height. However, it is also necessary to consider additional benefits of rhGH, including improvement in bone structure, body muscle/fat composition, and protein/lipid metabolism. Although continued growth may no longer be possible, some patients, such as those with GH deficiency, may benefit from rhGH therapy in adulthood since discontinuation of rhGH after final expected growth leads to deterioration in these other parameters.[21,35]

Ethical Issues

There is considerable controversy regarding the ethics of using rhGH for children with ISS. Therapy with rhGH should be considered from two perspectives: the goals of medicine and the well-being of the patient.

Goals of Medicine

Determining the congruence between the goals of medicine and the use of rhGH for children with idiopathic short stature is dependent largely upon the definitions of "disease" and "disability" and its application to short stature. A classic definition of health is the absence of disease, and from this perspective, disease and disability are defined as departures from "species-typical normal functional organization or functioning."[39] In the case of ISS, there is no pathological underpinning for the condition of short stature, or no documented subnormally functioning organ. Therefore, ISS would not be considered a disease or disability within the framework of these definitions. If ISS is not a disease or disability, the use of rhGH for this condition would be seen as an enhancement of human performance or appearance rather than as a treatment. Since enhancements do not give rise to an obligation to treat, the appropriateness of using rhGH for children with ISS is called into question.[39]

Others argue that in the case of ISS, the disease label is irrelevant. It is the physical condition itself (i.e., short stature) that is the handicapping and stigmatizing factor, regardless of whether it bears a disease label.[40] On this view, ISS need not be conceptualized as a disease or disability in order to warrant medical intervention.

Even if ISS is seen as a disease, it isn't clear that the use of rhGH is the appropriate response. All normal and healthy populations have genetic variation that will give rise to individuals with short stature and no underlying medical pathology. By definition, children with short stature relative to their peers will always exist and targeting the current cohort for medical intervention will merely replace them with another cohort. Some therefore assert that "it would be better to eradicate the bias against short individuals than to attempt to eradicate the condition of being short, which, in any event, is doomed to failure."[41] Similarly, since nearly all items within our environment are used commonly by males and females alike and male children with ISS are on average 5 inches taller than female children with ISS, targeting short children for interventions to improve their ease of functioning within our environment rather than altering the environment itself may not achieve desired results.[42]

The Well-Being of the Patient

There are several difficulties in defining and advancing the well-being of children with ISS. The use of rhGH in children with ISS increases growth rate and height and may minimally increase final height, as compared with baseline predicted values, but generally does not increase final height to normal levels. Some argue, however, that the major criterion for the use of rhGH should be improvement in the individual patient's quality of life, regardless of whether final height is improved or not. But, whether short stature itself (with no pathological basis) correlates with psychosocial dysfunction of any kind is debated. One study showed that the self-esteem and self-image of normal short children do not appear to be lowered as a result of their height and are no different between children who have used rhGH for 5 years and those who remain untreated.[43] Other studies indicate that the quality of life for normal short children is generally not reduced as compared with those of normal height or as compared with those of short stature receiving rhGH.[44,45] Evidence also shows that short children have social skills and problem solving abilities which are comparable to their peers[46]; that IQ and achievement scores did not change for children before and after the use of rhGH; and that short stature is not associated with clinically significant psychosocial problems, significant psychosocial adjustment problems or

dysfunction, or psychosocial or intellectual functioning.[47,48,49]

In contrast, other studies reveal that very short adolescents and adults have a significantly greater risk for psychological, cognitive, and sexual problems than peers of normal height. For example, one study found short stature in adults to be significantly associated with lower educational achievement, lower self-esteem, and greater emotional distress.[49] Some experts maintain, however, that these problems may be better addressed by psychological intervention and counseling than by the use of rhGH.

A second difficulty in advancing the well-being of children with ISS is that the rigor and invasiveness of daily rhGH injections for several years may foster the belief that normal stature is of utmost importance. Disappointing final results may then lead to psychological distress in some patients; nonetheless, others may be happy they have done everything they can to ameliorate their condition.[50] Regardless of final height, the growth spurt induced by rhGH may allow some adolescents to overcome concern about short stature and focus on other aspects of self-worth.

Finally, the patient's own assessment of therapy and its goals and burdens should normally be considered in deciding what is in his or her best interest. For children, however, parents generally decide what is in their child's best interest. In a 1999 editorial in the New England Journal of Medicine, Dr. Oberfield expresses concern about a medical practice that is based, in part, on biases from society and pressures from parents, sometimes influenced by their own ideals and expectations for their child(ren), and therefore suggest that the use of rhGH treatment for nonpathologic short stature may not be justified or reasonable.[43,50] Some call for tempering patient and parental expectations with regard to the effectiveness of rhGH for ISS.[4] Others assert that intervention for nonpathologic short stature is appropriate if the goal of therapy is to reduce the risk of psychological and social problems.[50]

Insurance Coverage

While no national Medicare coverage decision has been made specifically with respect to GH therapy, rhGH is subject to the identical policy established by HCFA for any other drug. According to this policy, if a drug is administered intravenously incident to a physician's service in accordance with its FDA labeling, coverage is approved. However, if a drug is capable of self-administration, whether by the oral, subcutaneous, or inhalation route, coverage is denied. This is only true in situations, however, where an alternative treatment exists. In the case of rhGH, there is no alternative treatment, so it is covered in its FDA approved capacities, those being the treatment of girls with Turner's syndrome, individuals with chronic renal insufficiency, and individuals with classic growth hormone deficiency. Medicaid has more leniency, and policies can be made at the state level by invoking the medical necessity provision of the Social Security Act.[52]

A 1998 study found that for cases of idiopathic short stature, only 10-13% of cases would be covered by insurers. However, 94% of cases of classic GH deficiency, 52% of cases of Turner's syndrome, and 58% of cases of chronic renal failure would be covered by insurers. There is currently a two- to four-fold mismatch between physician recommendation for and insurance coverage of rhGH.[5] Currently, insurance companies are covering off-label use of rhGH on a case-by-case basis. Total nationwide costs to the U.S. if all children with short stature receive rhGH

could exceed $18 billion annually (more than 95 % of the cost would be for children with ISS).[5]

Conclusions

- Growth Hormone therapy is both the standard of practice and FDA approved for children of short stature with classic GH deficiency, chronic renal failure, and Turner's syndrome.
- In comparison, for children with ISS, appropriate patient selection criteria, optimal rhGH regimen, and other treatment variables for rhGH have not yet been established.
- While the use of rhGH for ISS shows little risk of serious short-term harm, the long-term risks are not yet known.
- The benefits of the use of rhGH for ISS can not yet be determined. While rhGH appears to increase the growth rate of children with ISS, its effect on final adult height is not clear. There is also disagreement as to whether final height or some other criterion, such as accelerated growth, should be used to measure the benefit of the use of rhGH for ISS.
- The use of rhGH for ISS raises a host of controversial and unresolved medical and ethical issues.
- rhGH for ISS is not included in the coverage by many health plans.
- No cost-effectiveness data exist for rhGH for ISS.

Recommendations

- The long-term safety, efficacy, and cost-effectiveness of the use of rhGH for ISS should be established through additional studies.
- At this time, rhGH should be used for ISS only in controlled settings that generate data on the intervention's safety and efficacy.
- Individuals responsible for determining the benefits set for public and private insurance products should carefully weigh the value of rhGH for ISS as the safety and efficacy data evolve.
- Health professionals should help parents and children address the problems that stem from ISS.

Appendix I: FDA - Approval Status of rhGH Products

Note: Data provided by PDR (1997); The Pink Sheet (1995a); The Pink Sheet (1995b); The Pink Sheet (1995c); The Pink Sheet (1996a); The Pink Sheet (1996b); The Pink Sheet (1996c); The Pink Sheet (1997a); The Pink Sheet (1997b); The Pink Sheet (1998); The Blue Sheet (1996b).

rhGH Product (Generic Name; Manufacturer)	FDA-Approved Indications	Comments
Humatrope® (somatropin; Eli Lilly and Co., Indianapolis, IN)	Long-term treatment of children with growth failure due to inadequate endogenous GH secretion Treatment of children with chronic renal insufficiency until time of kidney transplant Treatment of short stature associated with Turner's syndrome in patients whose epiphyses are not closed Treatment of adults with adult- or childhood-onset somatropin (growth hormone) deficiency syndrome	
Serostim® (somatropin; Serono Laboratories, Norwell, MA)	Treatment of AIDS wasting and cachexia (orphan drug status with 7-year marketing exclusivity for this indication)	Studies underway to examine value for treatment of wasting in cancer and elderly patients and treatment of children with AIDS who show failure to thrive
Saizen® (somatropin; Serono Laboratories, Norwell, MA)	Treatment of children with growth failure due to inadequate endogenous GH secretion	Product identical to Serostim® manufactured by same company
Nutropin® and Nutropin-AQ® (somatropin; Genentech. Inc., South San Francisco, CA)	Long-term treatment of children who have growth failure due to inadequate endogenous GH	Studies underway to assess use of product in adults with adult- or childhood- onset GH deficiency

	secretion Treatment of children with growth failure associated with chronic renal insufficiency until time of kidney transplant Long-term treatment of short stature associated with Turner's syndrome	
Protropin® (somatrem; Genentech, Inc., South San Francisco, CA)	Long-term treatment of children with growth failure due to inadequate endogenous GH secretion	Other etiologies of short stature excluded
Genotropin® (somatropin; Pharmacia & Upjohn Co., Kalamazoo, MI)	Long-term treatment of children with growth failure due to inadequate endogenous GH secretion	Other etiologies of short stature excluded
Norditropin® (somatropin; Novo Nordisk, Denmark)	Long-term treatment of children with growth failure due to inadequate endogenous GH secretion	U.S. marketing temporarily blocked due to patent infringement claim filed by Genentech; claim dismissed by New York Federal Appeals Ccourt in March, 1997, allowing Norditropin to enter U.S. market; marketing applications planned for use in children with intrauterine growth retardation or renal transplants
Biotropin® (Bio-Technology General Corp.; Iselin, NJ)	Long-term treatment of children with growth failure due to inadequate endogenous GH secretion	U.S. marketing temporarily blocked due to patent infringement claim filed by Genentech

Appendix II: Summary of Studies on Human Growth Hormone for Children with Idiopathic Short Stature

****KEY****GHD, growth hormone deficiency; HV, height velocity (growth rate); ISS, idiopathic short stature; IU, international units; LVMI, left ventricular mass index; NA, not available; NS, nonsignificant; PAH, predicted adult height; rhGH, recombinant growth hormone; SC, subcutaneous; SDS, standard deviation score

Study/Sample Description	Procedural Protocol	Results	Conclusions/Comments
Rekers-Mombarg et al.(1998) 9 centers in The Netherlands, United Kingdom, Germany,France, Austria, Israel, and Spain 233 children with ISS and mean age of 10.1 years (boys) or 8.7 years (girls) at start of treatment	SC rhGH (Humatrope) 6 days a week at 3 IU/m^2/day (.2 mg/kg/week; n=73), 4.5 IU/m^2/day (.3 mg/kg bw/week; n=78), or 3 IU/m^2/day for 1st year and 4.5 IU/m^2/day thereafter (n=72) until the onset of puberty; results compared with untreated control group with ISS (n=229)	Mean height for age (SDS): Increase at end of years 1-4 among all treated subjects ($P \leq .001$ for each year); greater gain in 4.5 IU group than in 3.0 and 3/4.5 IU groups for year 1 (1.1, 1.3, and 1.0; P=.02 and <.001), year 2 (1.7, 2.0, and 1.6; P=.006 and .003), and year 4 (2.3, 2.3, and 2.4; $P \leq .05$) Mean HV (cm/year): Increase from 4.4 to 8.6 in year 1 (P <.001) and 6.8 in year 2 (P <.001); greater gain in 4.5 IU group than in 3.0 IU and 3/4.5 IU groups in year 1 (P=.009) but not year 2 Mean bone age (years): Gain of 2.4 at end of year 2 (NS) and 4.8 at end of year 4 (NS) among all treated subjects (NS); less accelerated growth in 3/4.5 IU group than in 3 IU and 4.5 IU groups (4.7, 4.9 and 4.8 at end of year 4; NS) Mean PAH: Gain	Among children with ISS, rhGH for 4 years increases body height, bone maturation, and PAH; however, these increases slow down after the 1st treatment year and this waning effect is not changed by increasing the rhGH dose; only the increase in body height is significant; and doses of 4.5 IU/m^2 bs/day induce somewhat better growth than doses of 3 IU/m^2 bs/day with or without a dose increase after the 1st year Prospective, dose randomization trial Supported by rhGH manufacturer High drop-out rate (43%)

		of 1.09 SDS by end of year 2 (P <.001) and 1.5 SDS by end of year 4 (NS); less gain in 3 IU group than in 4.5 IU and 3/4.5 IU groups (P=.006 and .008)	
Barton et al. (1995) Middlesex Hospital and Hospital for Sick Children, London, United Kingdom 29 prepubescent children with ISS	Daily SC rhGH (Genotropin) at 20 IU/m^2/week for[3] 1 year (standard-dose; n=10) or 40 IU/m^2/week for[3] 1 year (high-dose; n=10), or no rhGH for 1st year followed by low- or high-dose rhGH for 2nd year (controls; n=9)	Median height for bone age (SDS): Increase of .4 in standard-dose group (NS), 1.1 in high-dose group (P=.04), and .1 in controls (NS) at end of year 1; increase of .3 SDS in standard-dose group (NS) and 1.3 SDS in high-dose group (P=.006) at end of year 2 Mean HV (SDS): Increase of 2.7 in standard-dose group and 5.7 in high-dose group and decrease of 0.5 in controls at end of year 1 (P<.001); increase of 1.3 in standard-dose group and 2.8 in high-dose group at end of year 2 Bone age to chronological age ratio: Greater increase in standard-dose group than in high-dose group and controls during year 1 (ratio of 1.1, 0.7, and 0.6; NS) and in standard-dose group than in	In children with ISS, rhGH at a dose of 40 IU/m^2/week appears to promote a greater short-term increase in height and growth rate than a dose of 20 IU/m^2/week or no treatment and does so without excessive bone growth but with a significant increase in LVMI Prospective randomized trial Small study sample

		high-dose group during year 2 (ratio of 1.2 and 1.0; P£.05 and NS from baseline) Median LVMI: Increase only in high-dose group (P=.04) but still in normal range in all groups at end of year 2 Fractional shortening: No significant differences from baseline in any group or between groups	
Hintz et al. (1999) Several centers in the USA 80 prepubescent children with ISS and pretreatment height SDS or more than -2	SC rhGH at 0.3 mg/kg/week in 3 or 7 divided doses for 2-10 years Data compared with those of 3 historical groups not treated with rhGH: normal subjects with initial height SDS of -1 (n=291) or height SDS of -1 and bone age of < 10 years (n=37) or ISS subjects with initial height SDS of less than -2	Mean final height: 165.5 cm and 153.1 cm among rhGH-treated boys and girls, respectively (greater than initial PAH in 79% but still less than mean midparental height with average height SDS of -2.6 SDS) Mean gain over initial PAH: 5.0 and 5.9 cm in rhGH-treated boys and girls, respectively; 1.6 and 3.3 cm in untreated normal boys and girls, respectively, with initial height SDS of -1; -1.7 and 3.6 cm in untreated normal boys and girls, respectively, with initial height SDS of -1 and	In children with ISS, long-term rhGH therapy may increase final height to above initial predicted values and above final height in untreated ISS subjects although the increase is minimal Retrospective study with historical controls Study supported by manufacturer of rhGH product

		bone age of < 10 years; and 4.2 and 0.1 cm in untreated ISS boys and girls, respectively Initial PAH exceeded in 79% and 78% of rhGH-treated boys and girls, respectively, with ISS but only 18% and 5% of untreated boys and girls, respectively with ISS	
Wit et al. (1995) Several centers in The Netherlands 21 prepubescent children with ISS	Biosynthetic methionyl GH (Somatonorm; 1st 2 years of study) or rhGH (Genotropin) at 2 IU/m^2/day by SC injection 7 days a week; dosage maintained in subjects with HV gain of ³ 2 cm/year (n=10) but increased to 4 IU/m^2/day in those with HV gain of < 2 cm/year or HV reduction to below 50th percentile for bone age (n=17) Data compared with historical data from matched children with untreated ISS (n=27) or rhGH-treated GHD (n=7)	Mean height SDS for age: Improvement from -3.8 to -2.5 (P<.01) at 4 years and -2.3 (P<.01) at 6 years in treated ISS group and from -3.9 to -1.8 (P<.02) at 4 years in treated GHD group; no change from -3.2 to -3.4 at 4 years and -3.3 at 6 years in untreated ISS group Mean height SDS for bone age: NA for untreated ISS group; no significant change from baseline to 4 years or 6 years in treated ISS and GHD groups (-1.0, -1.5, and -1.1 and NA, -1.1, and -0.9, respectively) Mean PAH: Increase in SDS of .6 (NS) in treated group; NA for other groups	In children with ISS, rhGH therapy improves growth but does not generally improve final projected height, possibly because it increases bone maturation and shortens puberty Differences in response to rhGH in children with ISS may be due to differences in endogenous GH secretion and in initial bone age delay Small study sample Prospective trial with historical control

		Mean final height: No difference between treated and untreated ISS groups or 2nd untreated ISS group matched for bone age (159.2 cm, 160.6 cm, and 159.0 cm) Accelerated bone maturation in rhGH-treated groups and shortened duration of puberty in rhGH-treated boys Lower integrated concentration of GH and stimulated GH secretion predictive of better response to rhGH	
Kawai et al. (1997) Kyoto University, Kyoto, Japan 27 prepubescent boys with ISS	SC rhGH at .5 IU (17 mg)/kg/week (n=9) or no treatment (n=18); final height defined as height gain of < 1 cm during past year	Mean chronological and bone age at onset of puberty: 11.2 and 10.9 years for rhGH group and 13.0 and 10.7 years for control group (P<.05) Mean duration of puberty: 3.5 years in rhGH group and 5.5 years in control group (P<.01) Mean height for bone age: No difference between rhGH and control groups in SDS gain before puberty; SDS gain gradually reduced in rhGH group but constant in control	In boys with ISS, rhGH at a dose of .5 IU/kg/week does not improve final height and may instead reduce it by accelerating the onset of puberty and shortening its duration. Small study sample Controlled, retrospective study

		group during puberty (pubertal height gain of 20.5 and 28.8 cm, respectively; Mean final height: 154.2 cm in rhGH group and 162.0 cm in controls (P<.01)	
Wit et al. (1996) Several centers worldwide 151 children (101 boys, 50 girls) with ISS	GH at 0.5-1.0 IU/kg/week Data compared with those of 674 children (541 boys, 133 girls) with untreated ISS	Mean final height SDS: -1.4 to -2.6 among treated subjects (gain of 0.9 to 1.8 SDS over mean baseline height SDS; mean difference of -1.2 cm to +3.0 cm over mean initial PAH); -0.7 to -2.7 among untreated subjects (gain of 0.4 to 1.9 SDS over mean baseline height SDS; mean difference of -5.0 cm to +0.8 cm over mean initial PAH)	In children with ISS, final height remains just below initial PAH if not treated but improves minimally to just above initial PAH if treated with rhGH. Retrospective review with historical control
Loche et al. (1994) Ospedale Microcitemico, Cagliari, Italy 15 prepubescent children with ISS	SC GH at 0.5 U/kg/week (n=7) or 1.0 U/kg/week (n=8) in 4-7 doses for 4-10 years	HV: Gains of 4.1 to 6.6 cm/year in 0.5 IU group and 4.4 to 7.5 cm/year in 1.0 IU group after 1 year of rhGH; sustained increase in majority of patients in both groups (% not provided) during 4 years of rhGH with decline to pretreatment values thereafter Mean final height SDS: -1.6 in 0.5 IU group (gain of 0.9 over baseline	In children with ISS, long-term GH improves linear growth over baseline values for the first few years of treatment but does not improve final height over initial PAH Small study sample Retrospective study without similar untreated control group

		height SDS but loss of 1.2 cm over initial PAH); -1.4 in 1.0 IU group (gain of 1.0 over baseline height SDS without loss or gain over initial PAH)	
Herschkovitz et al.(1996) Soroka Medical University Center, Beer-Sheva, Israel 8 children (age, 6-12 years) with ISS	SC rhGH (Norditropin) at .1 IU/kg/day for 3 months	Increase in serum lipoprotein(a) at 2, 6, and 12 weeks of rhGH treatment (mean, 107%, 162%, and 153%; <.05) No significant treatment effect on plasma cholesterol, triglycerides, low-density lipids, or high-density lipids	In children with ISS, rhGH significantly increases serum lipoprotein(a) concentrations, although the clinical significance of this is not known at this time Small study sample Uncontrolled prospective study
Rekers-Mombarg et al. (1995) 9 centers in The Netherlands, United Kingdom, Germany, France, Austria, Israel, and Spain 34 children with ISS	SC rhGH (Humatrope) 6 days a week at 3 IU/m^2/day (n=9), 4.5 IU/m^2/day (n=13), or 3 IU/m^2/day for 1st year and 4.5 IU/m^2/day thereafter (n=12) for £ 4 years	All parameters of immune function within normal range before treatment but levels of immunoglobulin (Ig) above mean Gradual decrease in circulating leukocytes and lymphocytes with nadir at 6 months after start of rhGH (P=.003 and .006, respectively) followed by progressive increase thereafter in both then another decrease in lymphocytes to below pretreatment levels at 36 months (P=.001)	In children with ISS, rhGH may induce a reduction in leukocytes, lymphocytes, and immunoglobulin A, although the clinical significance of this is not clear Prospective, randomized trial Small study sample Patient overlap with Rekers-Mombarg et al. (1998) study

		No difference in neutrophil, eosinophil, basophil, or monocyte counts or CD4+ T-inducer to CD8+ T-suppressor ratio during treatment Transient decrease of IgA at 3 and 6 months (P=.001 and .002, respectively) but no change in IgM or IgG	
Spagnoli et al. (1995) Tor Vergata University and La Sapienza University, Rome, Italy 67 consecutive children (44 boys) with ISS	Daily SC rhGH at 12-16 IU/m^2/week; response to rhGH defined as gain in growth velocity of > 2.5 cm/year during 1st 6 months	HV gain of > 2.5 cm/year during 1st 6 months in 40 (60%) Predictors of response, as per univariate analysis, found to be bone age of -1.7 SDS for chronological age (P<.001), growth velocity of -2.1 SDS for chronological age and -2.3 SDS for bone age (P<.001), and ideal body weight of 106.2% (P<.01) at baseline Score obtained by formulated equation of pretreatment growth velocity and bone age (multivariate discriminant analysis) found to have sensitivity of 92.5% and specificity of 96.3% for predicting	Multivariate discriminant analysis of pretreatment growth rate and bone age may help identify children with ISS who are likely to respond to rhGH therapy Open prospective design Small convenience sampleTD>

		response to rhGH when applied to individual patients	

Appendix III: Search Strategy

Documents relevant to GH treatment in children were identified through a Medline search conducted in the MESH database (1995 to January, 28, 1999). Utilized keyword terms included growth hormone therapy and growth hormone treatment each separately combined with children, pediatric, children and growth hormone deficiency, children and somatropin deficiency syndrome, AIDS wasting, intracranial tumor, tumor, Turner's syndrome, Prader-Willi, Noonan syndrome, intrauterine growth retardation, renal insufficiency, short stature, juvenile arthritis, septo optic dysplasia, and Down syndrome, as well as somatropin therapy and somatropin treatment each separately combined with children and pediatric. The HAYES rating for quality of the literature is a C for idiopathic short stature, familial short stature, or constitutional delay (significant catch-up growth without proven improvement in final height).

Appendix IV: Government Agencies and Professional Associations

Food and Drug Administration (FDA): Recombinant human growth hormone products are FDA approved for use in children for the treatment of growth failure due to inadequate endogenous GH secretion, chronic renal insufficiency, and/or Turner's syndrome. One such product is approved for treatment of AIDS wasting and cachexia, although it is not clear if approval covers use in children. The use of rhGH in the treatment of clinical conditions not specifically reviewed and approved in the FDA's licensing process constitutes "off-label" use. Off-label use is legal, common practice and at the prescribing physician's discretion. However, a drug or biological product that is approved or licensed for marketing may not be marketed for the treatment of any but the approved indications and routes of administration. To evaluate the investigational status of a drug or biological for an off-label indication, published clinical research findings of the application in question must be considered. A summary of FDA-approval status of rhGH products is attached in Appendix I.

Health Care Financing Administration (HCFA): While no national coverage decision has been made specifically with respect to rhGH therapy, rhGH is subject to the identical policy established by HCFA for any other drug. According to this policy, if a drug is administered intravenously incident to a physician's service in accordance with its FDA labeling, coverage is approved. However, if a drug is capable of self-administration, whether by the oral, subcutaneous, or inhalation route, coverage is denied. This is only true in situations, however, where an alternative treatment exists. In the case of rhGH, there is no alternative treatment, so it is covered in its FDA approved capacities, those being the treatment of girls with Turner's syndrome, individuals with chronic renal insufficiency, and individuals with growth hormone deficiency. Although Medicare holds strictly to any national policies on these issues, Medicaid has more leniency, and policies can be made at the state level by invoking the medical necessity provision of the Social Security Act.[52]

American Academy of Pediatrics (AAP): In 1983, the AAP recommended use of

GH therapy only for children with classic GH deficiency. More recently, the AAP's Committee on Drugs and Committee on Bioethics (1997) expanded the recommendation to include children with chronic renal insufficiency, girls with Turner's syndrome, and children of very short stature whose ability to participate in basic daily-living activities is limited due to their stature and who have a condition for which growth hormone treatment is effective. The AAP does not recommend GH therapy for other short children. The long-term risks for this group are unknown and the efficacy of the treatment has not yet been determined. Even if research shows that there exists a positive risk-benefit ratio for this population, the overall benefit is still dubious. GH therapy may aid individual children, but it will never eliminate the relative measure of shortness altogether, and there will thus always be a group of shorter children who might suffer from prejudice. It is more appropriate to remedy the social prejudice against short people than to medically reinforce it through intervention or treatment. There is also the issue of economic justice. GH therapy is very expensive and will therefore be utilized primarily by high-income families rather than by low-income or disadvantaged children. This might serve to increase the burden on this population as children within this group may become disproportionately short. The widespread administration of GH therapy may result in the allocation of scarce funds for this type of procedure at the expense of primary health coverage. The AAP advocates additional research into possible risks and negative effects of GH therapy, actual expected increases in final height, and actual psychosocial benefits from any such increase. Pediatricians should be wary of commercial attempts to encourage parents to pursue GH therapy for their children.

American Medial Association (AMA): The AMA prepared two Diagnostic and Therapeutic Technology Assessment (DATTA) reports on the use of rhGH in children: one for short stature associated with Noonan syndrome[2] and one for short stature associated with Turner's syndrome.[53]

European Society for Pædiatric Endocrinology: The Society stated that rhGH "seems to be a remarkably safe drug when used in conventional substitution doses".[54] The Society reviewed studies regarding rhGH and carbohydrate metabolism, including glucose intolerance and insulin resistance[55], lipid and water metabolism [21], and immunological function [56], and found that rhGH treatment generally does not lead to undesirable clinical manifestations. However, the Society recommended that these functions continue to be monitored in patients receiving rhGH treatment, especially in those given supraphysiological doses or who may have predispositions to dysfunctions in these areas. The Society also recommended long-term observation that may provide the needed data to identify the final outcomes of rhGH treatment.[54]

Lawson Wilkins Pediatric Endocrine Society: Based on their evaluation of current literature, the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society established the following recommendations regarding rhGH therapy.[57]

- GH should be considered safe and effective in treating GH-deficiency based growth failure. It should be considered a standard of care for classically GH-deficient children; for children with subtler GH deficiency, a trial with rhGH should be considered, with careful monitoring and continuance only if effective.

- The safety and efficacy of rhGH therapy in normalizing growth in renal-

insufficient children before renal transplantation has likewise been established.

- Treatment of Turner's syndrome patients with rhGH appears promising and is likely to become a standard of care after more long-term data have been reviewed. The patients should not be evaluated for this therapy on the basis of GH tests.
- This therapy should not be used in children with constitutional growth delay, as it has not been demonstrated to be effective.
- Due to a lack of data, use of rhGH in patients with the following diagnoses can only be considered experimental: non-GH-deficient short stature, genetic short stature, intrauterine growth retardation, glucocorticoid-induced growth failure, renal transplantation, and Down, Noonan, and Prader-Willi syndromes. Treatment in ethically designed, controlled studies is the only currently acceptable application of this therapy to these diagnoses.
- Pituitary-derived GH should never be used.
- The initiation of treatment should consider the patient's and family's desires, expectations, and psychological health, with the aim of treatment being the long-term improvement of the patient's quality of life.
- A central system is needed for the reporting, evaluation, and dissemination of adverse effects of rhGH therapy.
- A pediatric endocrinologist or other physician trained in evaluating rhGH therapy progress and effects should oversee the treatment.
- Additional research, beyond application to additional diagnoses, is required in the following areas: psychological impact and age-and sex-specific norms of GH.

Appendix V: Public Comment

JANUARY 7, 2000

Ms. Brenda Holden
Health Technology Advisory Committee
121 East Seventh Place
Suite 400
P.O. Box 64975
St. Paul, MN 55164-0975

Dear Ms. Holden:

Re. The Use of Human Growth Hormone for Children with Idiopathic Short Stature

The following pediatric endocrinologists have reviewed the above-referenced "Preliminary Technology Evaluation Report: and agree with its contents:

David M. Brown

Antoinette Moran
Anna Petryk
Kumud Sane
Joseph Sockalosky
Martha Spencer
Christine Ternand

Sincerely,

David M. Brown, M.D.
Professor of Pediatrics and Laboratory Medicine and Pathology
Director, Division of Endocrinology
Director, General Clinic Research Center
University of Minnesota

JANUARY 24, 2000

Ms. Brenda Holden
Health Technology Advisory Committee
121 East Seventh Place
Suite 400
P.O. Box 64975
St. Paul, MN 55164-0975

Dear Ms. Holden:

Re. The Use of Human Growth Hormone for Children with Idiopathic Short Stature

It occurred tome and my pediatric encocrine colleagues when we reviewed the HTAC report on idiopathic short stature that the report should have referenced our community's published standard for the evaluation of children with short stature. I have enclosed a copy of that reference.

Sincerely,

David M. Brown, M.D.
Professor of Pediatrics and Laboratory Medicine and Pathology
Director, Division of Endocrinology
Director, General Clinic Research Center
University of Minnesota

Appendix VI: Summary of Guidelines for Diagnosis, Monitoring, and Treatment

Diagnosis
Accurate, reliable, and standardized measurements of heightare recommended at every well-child visit or at 1-year intervals. From these data, growth velocity can be calculated

- Short Stature Requiring Close Monitoring (6 to 12 month intervals)
    1. Height < 5th percentile for age.
    2. Growth percentiles decreasing.

3. Less than 1.75 inches or 4.5 cm growth per year in children over 4 years of age.

- Short Stature Requiring Differential Diagnosis and Evaluation
  1. Height < 3rd percentile for age (> 2 standard deviations from mean).
  2. Height < 5th percentile for age, and growth velocity < 10th percentile for age measured over at least 6 months.
  3. Growth < 3rd percentile for age measured over a 1 year period, regardless of present height.

- **History**
  - expected adult height.
  - growth histories of parents and siblings
  - medical history including birth history, birth weight, and perinatal aberrations in growth.
  - any history of serious infections, injuries, or radiation
  - evidence of development delay, neurological problems, or psychosocial deprivation.
  - gastrointestinal function including dietary history, appetite, and elimination should be explored.
  - chronic systems illness i.e.(cardiac, pulmonary. or renal).
  - medication history.

- **Physical Exam**
  - puberal development accessment
  - growth of extremities or trunk, congenital syndromes, other dysmorphic syndromes

- Laboratory Evaluation
  If signs and symptoms of chronic disease are not present.
  1. Blood count with sedimentation rate.
  2. Blood urea nitrogen, serum creatinine, electrolytes (including bicarbonate).
  3. Calcium, phosphorus, alkaline phosphatase.
  4. Endomysial antibodies (screening for celiac disease).
  5. Urinalysis and urine culture.
  6. Serum thyroxine, thyroid stimulating hormone and tri-idothyronine resin uptake.
  7. X-ray evaluation of skeletal maturation.

  If screening workup is negative, referral to a pediatric endocrinologist is indicated.

Consideration of GH Therapy Vary and are Based Upon Categories

- Classical Growth Hormone Deficiency
- Functional Growth Hormone Deficiency
- Turner Syndrome
- Previous Cranial Irradiation, or Acquired Pituitary or Hypothalamic Lesions
- Other Causes

Criteria for Discontinuing GH Therapy

- After the First 6 to 12 Months

1. < 50% increase in growth velocity.
2. Inadequate compliance.
3. Significant side effects.

Children who require exogenous GH to prevent hypoglycemia must continue GH therapy regardless of growth response.

- Final Discontinuation
  1. Growth < 2.5 cm per year.
  2. A height within the midparental height range.
  3. Inadequate compliance.
  4. Significant side effects.
  5. Bone age > 14 years in girls and > 16 years in boys.
  6. The patient or family decides to discontinue treatment.

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