UPDATE OF GUIDELINES FOR THE USE OF GROWTH HORMONE IN CHILDREN: THE LAWSON WILKINS PEDIATRIC ENDOCRINOLOGY SOCIETY DRUG AND THERAPEUTICS COMMITTEE

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The Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee guidelines for the use of growth hormone were first published in 1983, near the end of the era of human pituitary-derived growth hormone (GH), and again in 1995, a decade after the introduction of recombinant human (rh)GH.[1] The Lawson Wilkins Pediatric Endocrine Society also endorsed an international consensus document led by the Growth Hormone Research Society published in 2000.[2] This report serves to update those guidelines with an emphasis on new recommendations. The recommendations included here are limited primarily to the use of GH in infants, children and adolescents.

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FDA-APPROVED USES OF GH

Recombinant human GH has replaced human pituitary-derived GH, which should no longer be used because of the risk of contamination with the Jakob Creutzfeld prion. By 1995, the Food and Drug Administration (FDA) had approved GH therapy for short stature in the following conditions for which efficacy has been shown and much experience has been gained:

1. Growth hormone deficiency (GHD)/insufficiency
2. Chronic renal insufficiency pretransplantation
3. Turner syndrome

Since 1995, the FDA has approved GH for five additional indications:

1. Adults with GHD
2. Adults with AIDS wasting
3. Short stature from Prader-Willi syndrome (PWS)
4. Children with a history of intrauterine growth restriction (small for gestational age [SGA]) who have not reached a normal height range by age 2 years
5. Children with idiopathic short stature who are >2.25 SD below the mean in height and who are unlikely to catch up in height.

DIAGNOSIS OF GHD

The diagnoses of Turner syndrome, PWS, chronic renal insufficiency, and SGA are generally straightforward based on genetic testing, renal function, and/or birth data coupled with auxology. However, considerable variability exists in the diagnosis of GH deficiency, which remains a clinical challenge.[3,4] This is related to the continuum between severe GHD

FDA	Food and Drug Administration	IGF-I	Insulin-like growth factor I
GH	Growth hormone	IGFBP3	Insulin-like growth factor binding protein 3
GHD	Growth hormone deficiency	PWS	Prader-Willi syndrome
GHRH	GH-releasing hormone	SGA	Small for gestational age
HIV	Human immunodeficiency virus		

and normality, marked variability in GH assays, arbitrary "cutoffs" conventionally used to define GH deficiency on the basis of GH stimulation tests, and the lack of reproducibility of GH stimulation tests.[5,6] Consensus guidelines for the diagnosis of GH deficiency have been published.[2]

GHD should be suspected in a child with persistently subnormal growth rate with no other identifiable cause, in whom hypothyroidism, chronic illness, undernutrition, and genetic syndromes have been excluded. No gold standard exists for the diagnosis of GHD. Although children severely affected by GHD fail GH stimulation tests, there is no doubt that some children with GHD achieve stimulated GH concentrations above the arbitrary cutoffs that have been applied.[5] A trial of GH therapy should be approved for children with otherwise unexplained short stature who pass GH stimulation tests, but who meet most of the following criteria: (1) height >2.25 SD below the mean for age or >2 SD below the midparental height percentile; (2) growth velocity <25th percentile for bone age; (3) bone age >2 SD below the mean for age; (4) low serum insulin-like growth factor 1 (IGF-I) and/or insulin-like growth factor binding protein 3 (IGFBP3); and/or (5) other clinical features suggestive of GHD. In addition, the discovery of pituitary stalk agenesis, empty sella, sellar or supra-sellar mass lesion, or ectopic posterior pituitary "bright spot" on magnetic resonance image or computed tomography[5,7,8] in the context of clinically suspected GHD should be an indication for the diagnosis of GHD without the absolute necessity for stimulation tests. GH stimulation tests are optional in a child with growth failure who has evidence of additional pituitary hormone deficiencies, in patients with a history of surgery or irradiation in the region of the hypothalamus and pituitary, or in adequately nourished children with hypoglycemia coupled with clinical evidence of GHD and low serum growth factors. Conversely, GHD is unlikely in the presence of serum IGF-I concentrations at or above the mean for age. GH stimulation tests are not necessary before initiating GH therapy in children with Turner syndrome, chronic renal insufficiency, PWS, and children with short stature secondary to being born SGA. Additional pituitary functions should be evaluated in children diagnosed with GHD.

ADULT GHD

The approval for adult GHD is based on evidence that GH can reverse some of the abnormalities in body composition (increased total body fat, decreased lean body mass) and elevation in serum cholesterol seen in adult GHD. Subsequent studies have demonstrated improvements in bone mineral density, cardiac function, and quality of life in adult patients with GHD treated with GH.[9-13]

AIDS WASTING

GH is approved for adults (but not children) with AIDS wasting.[14] Recently a multicenter study was launched under the auspices of the Pediatric AIDS Clinical Trials Group to determine the efficacy and safety of GH in children with HIV.

PRADER-WILLI SYNDROME

Studies of four years' duration have demonstrated GH-induced alterations in body composition (decreased body fat and increased lean body mass) and increased linear growth in children with PWS.[15-19] Many of these children appear to have GHD, although this should be interpreted in the context of the patients' body mass index because short, nonobese children with PWS may not have biochemical evidence of GHD. Dosages used have varied in different studies. Higher doses may be necessary to sustain improvements in body composition.[19] Thus far, GH therapy has not increased the risk of diabetes mellitus in these children, but this remains a theoretical concern.

SUSTAINED POSTNATAL GROWTH FAILURE IN CHILDREN WHO HAVE BEEN SGA

Studies up to six years in duration have demonstrated that GH treatment of children with sustained postnatal growth failure secondary to intrauterine growth restriction (used synonymously with SGA in this communication) increases growth rate and stature.[20-24] Although extensive adult height data have not yet been reported, a recent randomized study looking at the effect of GH therapy for 2.7 ± 0.6 years on short adolescents born SGA demonstrated an increase in near adult height of 0.6 SDS (2.7 cm for males and 4.2 cm for females) in the treated group.[25] Doses used in these studies have been substantially greater than those used for other indications, suggesting a degree of GH resistance in this condition.[24] Thus far, these GH doses have not been found to induce carbohydrate intolerance, but this remains a concern, particularly in these patients who tend to develop insulin resistance, glucose intolerance, and type 2 diabetes mellitus later in life.

IDIOPATHIC SHORT STATURE

GH was recently approved by the FDA for children with idiopathic short stature who are >2.25 SD below the mean in height and who are unlikely to catch up in height. The predicted adult heights of children in this group were <63 inches for boys and <59 inches for girls. This approval is based on one randomized placebo controlled study and a second dose–response study in children with idiopathic short stature demonstrating an increase adult height or predicted adult height of from 1.5 to 3 inches.[26,27] At the time of this writing, a complete form of these reports have not been published in a peer-reviewed format. Exclusion of other causes of short stature in this setting must be stressed. Consideration for treatment should occur only after accurate diagnosis, careful monitoring of growth velocity and estimation of final height by a pediatric endocrinologist. Patients treated for idiopathic short stature should be enrolled in a database to monitor outcome. The long-term consequences of treating otherwise healthy children with GH remain uncertain.

INVESTIGATIONAL USES OF GH

Recent studies have suggested a potential role for GH therapy in a variety of additional conditions. A placebo-controlled study demonstrated a reduction in disease-related symptoms in adults with Crohn's disease.[26] Another study demonstrated an anabolic effect of GH in children with glucocorticoid-dependent Crohn's disease.[27] Uncontrolled studies have demonstrated short-term improvements in growth velocity in children with glucocorticoid-induced suppression of growth in other disorders, but no long-term data are available.[28,29] Larger, long-term studies are needed to determine the efficacy and safety of GH in these populations of children, bearing in mind the potential of the combined use of GH and glucocorticoids to induce carbohydrate intolerance.

Prospective studies have shown an anabolic effect and/or an increase in linear growth in *prepubertal* children with cystic fibrosis treated with GH.[30-34] In these studies, glucose intolerance has not been found. However, further study is needed, particularly in adolescent patients with cystic fibrosis because this population frequently develops diabetes mellitus as a result of pancreatic fibrosis. Larger, long-term studies are underway to determine whether these findings can be generalized, and whether an increase in growth is associated with an improvement in pulmonary function.

Studies examining the efficacy of GH therapy on growth in children with idiopathic short stature have demonstrated a small increase in growth velocity and adult height (approximately 5 cm)[35,36] in some. However, it is difficult to determine whether GH treatment increases adult height in any such person in a clinically significant manner. Thus, GH therapy is not indicated in idiopathic short stature without evidence of abnormalities of the GH-IGF axis.

SAFETY ISSUES

The safety of GH therapy was evaluated in a Growth Hormone Research Society consensus conference published in 2001 and endorsed by the Lawson Wilkins Pediatric Endocrine Society.[37] A review of the safety of childhood GH therapy was recently published.[38] Established and potential side effects of GH are listed in Table I. Overall, adverse effects of GH therapy occur in fewer than 3% of treated children compared with ~10% of adults.

"Benign" increased intracranial pressure (pseudotumor cerebri) may occur with GH therapy.[39] It is generally reversible with discontinuation of GH treatment. Often, treatment with smaller doses of GH can be reinitiated in children with intracranial hypertension without recurrence of symptoms. Similarly, transient sodium retention and edema may be seen at the time of initiation of GH therapy. In contrast to adult patients, severe edema and carpal tunnel syndrome are extremely rare in pediatric patients treated with GH. Breast development has been reported in children receiving GH therapy.[40] GH may induce carbohydrate intolerance in children with compromised insulin secretion.[41]

Slipped capital femoral epiphysis and worsening of existing scoliosis tend to occur in rapidly growing children and may occur as a function of rapid growth rather than as a direct side effect of growth hormone per se. In general, continuation of GH therapy is recommended. Although an increase in pigmented nevi was initially reported as a side effect of GH therapy,[42,43] more recent studies have not found such an increase in GH-treated patients.[44,45] Initial concern that GH might increase the rate of rejection of renal transplant recipients has not been substantiated by long-term studies.[46]

Table I. Adverse events associated with GH therapy

Intracranial hypertension (pseudotumor cerebri)
Edema
Slipped capital femoral epiphysis
Worsening of scoliosis
Gynecomastia
Hyperglycemia
Malignancy?

Concern has been raised regarding whether GH therapy increases the risk of leukemia and solid tumors. Current data indicate that any increased risk of leukemia is limited to children with underlying conditions that *already* predispose them to develop malignancies.[47] Epidemiologic studies have suggested an association between elevated serum IGF-I concentrations and breast, prostate, and colon cancers,[48] and some studies have suggested an increased incidence of colonic polyps and carcinoma in patients with acromegaly.[49,50] A recent retrospective analysis of cancer incidence and mortality rates in adults who received human pituitary-derived GH as children in the United Kingdom between 1959 and 1985 suggested an increased incidence of colon cancer and an increased mortality rate from colon cancer and Hodgkin's disease.[51] However, this conclusion was based on only two cases of each type of malignancy and, therefore, the significance of this finding remains tentative and requires larger, long-term studies for validation.[52]

Children receiving GH, who have had a malignancy, account for approximately 20% of patients treated with GH. Existing evidence indicates that GH treatment does not increase tumor recurrence in persons successfully treated for their primary lesion.[53] However, prudence would dictate waiting one year after completion of tumor therapy with no evidence of further tumor growth before initiating GH therapy in this group of children. All subjects who have been treated for a malignancy are at risk for a second malignancy. One study has suggested an increased risk of second neoplasms in children with a history of leukemia who were subsequently treated with GH.[53] Therefore, ongoing surveillance of such patients for second malignancies is important. Patients with neurofibromatosis type 1, Down syndrome, Bloom syndrome, and Fanconi's anemia carry an intrinsic risk of malignancies developing. Such children should be monitored carefully with regard to tumor formation if treated with GH. Patients with craniopharyngiomas may be treated with GH once the craniopharyngioma has been adequately controlled or stabilized.

Table II. Dosage recommendations for GH

Clinical condition	Dose (μg/kg/day)
GHD	
Children	25-50
Adolescents	25-100
Adults*	6-25
Chronic renal insufficiency	50
Turner syndrome	50
SGA	50-70
PWS	35-50

*Titrate dose to maintain serum IGF-1 concentration in the normal range for age and sex.

The use of high doses of GH in an attempt to reverse the catabolic effects of critical illness in non-GHD adults resulted in a dramatic increase in mortality.[54] Nevertheless, it is currently believed that *replacement* doses of GH should not be discontinued in GHD children admitted to the hospital, including intensive care.[55]

Recently, the LWPES Drug and Therapeutics Committee has been made aware of 7 patients with PWS who died a median of 13 weeks (range, 2-33 weeks) after starting on GH. Eiholzer et al reported 2 cases of sudden death in patients with PWS recently started on GH therapy.[56,57] Subsequent review of postmarketing surveillance databases revealed 5 additional cases of death from among approximately 675 children with Prader-Willi syndrome treated with GH since 2000 (personal communication, Bert Bakker, Kabi International Growth Study). The deaths have been associated with respiratory problems and/or were unexpected. Most have occurred in very obese males (mean weight for height 202%; range, 145-259%). In the absence of natural history studies of mortality rates in PWS, it is difficult to know the significance of this information because it is not known whether the deaths with GH treatment represent a change from baseline. Conceivably, GH therapy might exacerbate an underlying condition in a subset of patients with PWS. GH and IGF-I have been proposed to lead to increased lymphoid tissue growth in some cases. Tonsillar and adenoidal hypertrophy could contribute to sleep apnea,[58] which might offset the improvements in respiratory function reported to occur with GH therapy in PWS.[59] Until further data is available, caution is urged in the use of GH in very obese patients with PWS, particularly in those with respiratory problems including upper respiratory obstruction. In particular, children with PWS and clinically significant obstructive airway disease or apnea, gastroesophageal reflux with poor airway protection, morbid obesity, or uncontrolled weight gain, may need attention to these medical issues before being considered for GH therapy.

GROWTH HORMONE PRODUCTS

Multiple preparations of GH are available. Overall, there are no observable differences in the results obtained among the different preparations as long as the regimen follows currently approved daily injections. Many of the products are available in a variety of injection devices that are meant to make administration more appealing and easier. At this time, there is no evidence that clinical outcome differs among the various injection systems, although there may be patient and parent preference for some of these devices.

The FDA has also approved GH-releasing hormone (GHRH) for use in GHD. Evidence suggests that the approved dosing regimen for GHRH is less effective than GH and GHRH has been withdrawn from distribution as therapy for GHD. The FDA has also approved a depot GH preparation that is given every 2 to 4 weeks. Although a longer-acting GH is an attractive concept, the preparation and doses approved at this time, when given every 2 to 4 weeks, do not appear to increase growth velocity as well as daily GH injections, although a head-to-head comparison has not been reported. Studies are ongoing with this and other preparations given as weekly injections.

DOSING OF GH

Children with GHD may be treated once magnetic resonance imaging or computed tomography has excluded an intracranial mass lesion. GH should be administered subcutaneously on a daily basis and the dosage of GH should be expressed in μg (or mg)/kg/day. GH is routinely used in the range of 25-50 μg/kg/day in prepubertal children. A dose-response relationship in terms of height velocity in the first two years of treatment has been clearly demonstrated within this range. In prepubertal males with GHD[60] and in pubertal children with GHD,[61] doses as high as 100 μg/kg/day are effective and the FDA has approved this higher dose for pubertal children with GHD. Prediction models of growth response may be useful for determination of the optimal individual dose and are currently being investigated.[62]

Dosage recommendations based on published data and on FDA guidelines for use of GH in various indications are given in Table II. In children with renal failure, attention should be directed to factors that interfere with growth, such as acidosis, inadequate caloric intake, and uncontrolled secondary hyperparathyroidism, before consideration for GH therapy. Higher doses may be required for children with growth failure secondary to intrauterine growth restriction.[24]

RECOMMENDATIONS FOR MONITORING AND DOSE ADJUSTMENTS

The routine follow-up of pediatric patients receiving GH should be performed by a pediatric endocrinologist in partnership with the pediatrician or primary care physician. Children should be evaluated every 3 to 6 months. Increase in height and height velocity are the most important indicators of response to GH. For comparative purposes, data should be expressed as the increase in (or Δ) height SDS for age and sex.

Adequate response to childhood GH therapy is shown by an increase in linear growth velocity within the first six

months. It is helpful (but not essential) to have an accurate pretreatment growth velocity with which to compare the response. More definitive evidence of GH efficacy is the change in height SDS over the first year of therapy, which in children with GHD is typically an increase of at least 0.25 SDS. In addition, effective therapy is generally associated with normalization of the IGF-I level.

For assurance of compliance, dosing and perhaps, safety considerations, yearly monitoring of serum IGF-I and IGFBP-3 levels is useful, particularly in light of the associations between elevated serum IGF-I and certain cancers.[48] Patients with prior childhood cancer or with a diagnosis that predisposes them for malignancy should be monitored closely for malignancy. Monitoring free T_4 and TSH is of value for detecting hypothyroidism, which may appear during GH therapy. When impaired carbohydrate tolerance is suspected, measurement of fasting blood sugar and hemoglobin $A1_C$ is indicated. Routine monitoring of GH antibodies during GH therapy is unnecessary. Complete blood counts, lipid profiles, serum leptin, bone markers, fasting serum insulin levels, and bone ages need not be monitored routinely in the child receiving GH therapy.

For patients who display a suboptimal growth response or in whom the IGF levels remain low with assurance of compliance with the injection schedule, it is reasonable to increase the GH dose within the FDA approved dose guidelines (Table II). Dose reductions should be considered for patients with serum IGF-I levels substantially above the normal range after the first two years of therapy.

Further treatment is generally futile if no increase in growth rate or serum IGF concentration over baseline is detected within the first 6 to 12 months in a compliant patient receiving an appropriate dose of GH. Treatment with supraphysiologic doses of glucocorticoids or concurrent hypothyroidism may interfere with growth response. It is extremely rare that anti-GH antibodies, which attenuate the growth response, may develop. Growth response in pubertal patients may be difficult to interpret, because growth rates increase spontaneously during puberty, even without GH treatment.

TRANSITION FROM PEDIATRIC TO ADULT USE OF GH

Often idiopathic GHD does not persist into adult life, whereas organic GHD usually does. GH has major metabolic actions, which are important for body composition, bone mineral density, and general health in adults as well as in children. Therefore, repeat screening for GHD[63] is advisable after GHD children reach adult height. Such testing should be undertaken after an interval of 1 to 3 months off GH therapy. Because the criteria for adult GHD are more stringent (peak GH <5 ng/mL) than for childhood GHD, approximately 70% of children with idiopathic isolated GHD who met criteria for childhood GHD by stimulation testing do not meet criteria for adult GHD upon retesting.[64] Patients with multiple pituitary hormone deficiencies, those with genetic defects of GH synthesis, and those with severe organic GHD can be excluded from repeat testing for GHD. Therapy in these adolescents should be maintained without interruption after completion of linear growth.

Although there is little information on this issue in adolescents with GH deficiency who have completed growth, current data suggest that when the diagnosis of adult GHD is established, resumption or continuation of GH therapy is recommended to achieve optimal body composition, lipid profile, and cardiac function.[65,66] Dosages of GH recommended for adults with GHD are substantially lower than for children with GH (Table II) and side effects are more common (Table I). It is recommended that GH doses be gra dually reduced after epiphyseal closure, using serum IGF-I concentration as a guide with the aim of maintaining serum IGF-I levels within the age-appropriate normal range. The transition to adult GH replacement should be arranged as a close collaboration between the pediatric and adult endocrinologists who should discuss the issues related to reinitiation or continuation of treatment with the patient.

Caution should be used when considering the decision to continue GH therapy in conditions where there is a known risk of diabetes or malignancy. There is currently no evidence that GH therapy benefits adults other than those with GHD or AIDS wasting.

CONCLUSIONS

Recombinant human GH is an important pharmacologic agent to stimulate linear growth and improve body composition in children with GHD and to increase linear growth in children with chronic renal failure, Turner syndrome, PWS, and those with postnatal growth failure secondary to having been born SGA. Side effects are uncommon and often reversible with discontinuation of GH or a reduction in dose. Although recently approved by the FDA for severe idiopathic short stature, the impact of GH treatment on this population remains unclear and this approval should not obviate the need for a thorough investigation of the cause of the short stature. Studies are currently underway to determine whether GH may improve anabolism and/or increase linear growth in children with other conditions such as cystic fibrosis, AIDS, and glucocorticoid-dependent inflammatory bowel disease. Use of GH in these latter conditions remains investigational. Although generally safe, GH has potential side effects. Children receiving GH must be monitored closely by physicians who are experienced with its use.

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