Growth Hormone Use in Pediatric Growth Hormone Deficiency and Other Pediatric Growth Disorders

Based on presentations by Ron Rosenfeld, MD; David B. Allen, MD; Margaret H. MacGillivray, MD; Craig Alter, MD; Paul Saenger, MD; Henry Anhalt, DO; Ray Hintz, MD; and Harvey P. Katz, MD

Presentation Summary

The diagnosis and management of growth disorders in children, particularly disorders that respond to therapy with growth hormone (GH), raise challenging clinical and economic issues. Several such issues are presented in the following article in which Dr. Ron Rosenfeld examines the evaluation and diagnosis of the child with short stature; Dr. David B. Allen discusses the anabolic and metabolic indications for GH treatment in children; Dr. Margaret H. MacGillivray reviews GH dosing, height outcomes, and follow up; and Dr. Craig Alter presents the payer's perspective on the diagnosis and treatment of pediatric GH deficiency.

In addressing the use of GH in other pediatric populations, Dr. Paul Saenger focuses on Turner syndrome, Dr. Henry Anhalt on chronic renal insufficiency of childhood, and Dr. Ray Hintz on idiopathic short stature. Dr. Harvey P. Katz presents one managed care organization's policy and implementation plan that is used to guide decisions regarding coverage for GH treatment.

Payer Highlights

- Concrete policies/guidelines on the use of GH that are authored by endocrinologists would assist managed care plans in making coverage decisions that are consistent with the endocrine society.
- Guidelines must allow for flexibility to determine coverage on a case-by-case basis, with regard to new indications and technology.
- Case review process must be refined:
  - Payers require detailed patient history from clinicians to determine whether coverage for GH therapy should be approved.
  - A review committee comprising an endocrinologist, a medical director, and a payer could examine efficacy and safety of treatment in each case, and whether the decision to cover is fair and ethically sound as well as update guidelines periodically to reflect developments in the endocrine community.

Growth in humans is an exceedingly complex biologic process, and growth disorders, which are most apparent in childhood, are equally complex. The diagnosis and management of such disorders pose challenging clinical and economic issues; several of which are explored in the following presentations.

Evaluation and Diagnosis of the Child With Short Stature

When evaluating a child with short stature, the pediatric endocrinologist often integrates multiple clinical and laboratory data, as is done with any other endocrine diagnosis, rather than relying only on the results of a particular biochemical assay.

Evaluation for growth hormone (GH) deficiency in a child who is short (ie, whose height is more than 2 standard deviations [SDs] below the mean) should not be initiated until other causes of growth failure, such as hypothyroidism, chronic systemic disease, Turner syndrome, or skeletal disorders, have been excluded. A comprehensive clinical and auxologic assessment, combined with a bone-age X ray and biochemical tests of the GH/insulin-like growth factor (IGF) axis, is then warranted. The auxologic assessment consists primarily of a careful evaluation of the child's growth rate and velocity and family history of growth and height patterns.

GH, a major peptide hormone, is secreted by the anterior pituitary. It binds to a transmembrane receptor and eventually leads to the production of at least 3 GH-dependent peptides: IGF-1, IGF binding protein-3 (IGFBP-3), and the acid-labile subunit. These 3 peptides combine to form the major circulating form of IGF, which is delivered to the target cell, binds to an IGF-1 receptor, and stimulates skeletal growth.

Because GH is normally secreted in a pulsatile manner, with very low levels seen during the day and 6 or 7 spontaneous spikes most commonly occurring during deep sleep, clinicians cannot rely on a random blood sample for GH level measurement. Instead, endocrinologists have stimulated the pituitary gland pharmacologically (eg, with insulin) or physiologically (via exercise or sleep) to secrete GH to observe how well the gland responds. However, even in normal individuals rendered hypoglycemic by intravenous insulin, the increase in GH levels in response to hypoglycemia varies considerably, from an arbitrarily defined, and assay-dependent, normal level of at least 10 ng/mL to levels that are several times higher.

The arbitrary nature of such provocative testing is illustrated by a study in which spontaneous GH secretion was measured via an indwelling intravenous line every 20 minutes over a 24-hour period in 2 normal short children (normal on the basis of provocative GH levels of greater than 10 ng/mL) and 2 children diagnosed with GH deficiency (GH deficient on the basis of provocative GH levels less than 10 ng/mL). Although 1 GH-deficient child had little measurable GH, the other exhibited 2 spontaneous peaks of 20 ng/mL and a GH profile that was indistinguishable from those of the 2 normal short children.

The tests rely on an arbitrary definition of what constitutes a normal or subnormal response, the assays used to measure response are not standardized and have poor reproducibility, and the response to testing is age dependent in children and adults. In addition, test results are affected to some extent by sex steroids. Thus, criteria used to diagnose prepubertal and pubertal children must be reconsidered. Because such tests lack bimodal distribution, they are limited in their capacity to identify partial GH deficiency. Those tests also are uncomfortable, expensive, and at times involve an element of risk to the patient.

An alternative approach is to consider the 3 plasma components of the IGF system that are GH dependent (IGF-1, IGFBP-3, and the acid-labile subunit) in addition to GH measurements. However, measurement of the IGF components also has limitations. For example, IGF-1 levels in children are markedly age dependent; very low levels are observed in young children. Moreover, comparisons between the results of IGF-1 assays and GH provocative tests are not 100% concordant. Although most children who have failed provocative testing also have a low IGF-1 level, some children with low GH levels have a normal IGF-1 level. Similarly, many children with idiopathic short stature have a normal GH level but a low IGF-1 value. As is the case with GH levels, there is no bimodal distribution of IGF-1 concentrations and no clean separation of abnormally low levels from lower limits of normal. Although more normative IGF-1 data would be of value, it is likely that clinicians are dealing with a continuum of GH-IGF secretion, and sharp discrimination between GH deficiency and borderline GH-IGF production may not be possible.

This is also the case with the IGFBP-3 level. Although many children with classic GH deficiency exhibit very low levels of IGFBP-3, some have a normal IGFBP-3 value. Again, there is not 100% concordance in the results of IGFBP-3 assays and GH tests.

The inability to reconcile the results of GH and IGF tests may be related more to the inadequacies of GH testing than to the relevance of IGF measurements. At present, ample data support the primacy of IGF determinations in truly defining the endocrine milieu of a pediatric patient. However, it is probably unrealistic to expect—or to have ever expected in the past—that a biological process as complex as growth can be reduced to 1 or 2 simple diagnostic tests.

At this time, the diagnosis of GH deficiency in children with short stature may need to be based on auxology and supported by either provocative GH testing or careful determinations of the IGF system. That approach may result in some overdiagnosis and overtreatment, both of which are preferable to failing to diagnose or to treat appropriate children during a window of time that will allow them to grow.

Anabolic and Metabolic Indications for GH Treatment in Children

In addition to promoting linear growth, GH has considerable and favorable physiologic effects on adipose tissue, bone metabolism, and muscle accretion. During childhood, GH stimulates the proliferation of adipose precursor cells, restricts their differentiation into mature adipocytes, stimulates hormone-sensitive lipase (the rate-limiting step for lipolysis), and limits deposition of fat in the abdominal visceral depot. Normal secretion of GH also promotes accretion of lean body mass, increases muscle weight and nitrogen retention (both directly and indirectly via IGF-1), and appears to influence normal muscle fiber distribution between type 1 and type 2 muscle fibers. Moreover, because GH and IGF-1 receptors are expressed in various sites in bone, GH directly stimulates osteoblast and osteoclast differentiation and promotes the accretion of bone mass during childhood and adolescence. Consequently, children with severe GH deficiency demonstrate reduced linear growth and reduced lean body mass, increased body fat (particularly as a disproportionate deposition of visceral and truncal fat), subnormal bone density, and a tendency to develop lipid abnormalities.

Traditionally, the indications for GH therapy in childhood have been

judged by growth impairment and target height goals. Therefore, normally growing GH deficient children, such as those who have undergone craniopharyngioma removal, often do not receive GH therapy. However, increased knowledge about the different physiologic effects of GH has raised several issues, primarily that of weighing the benefit of treatment against its risks, its costs, and the possible treatment-related morbidity. Although the value of GH therapy in adults with GH deficiency has been recognized and such treatment has been approved because of its beneficial effects on body composition and lipid profiles, this is not yet the case in children with GH deficiency. However, the principles used to determine the value of treatment for adults with GH deficiency should be applied to children as well.

Body Composition. Children undergoing surgery to remove a craniopharyngioma demonstrate a well-known phenomenon of growth without GH. Often, they receive no GH therapy after surgery because there is no height-related indication for such therapy. However, because many such children exhibit markedly abnormal body composition (most notably, truncal obesity) despite normal or near-normal height for their age, it is highly likely that the lack of GH is responsible for the increase in fat mass and the reduction in lean body mass.

Body composition studies are performed to determine how to make the transition from GH therapy in childhood to possible GH therapy in adulthood. However, the effects of GH on body composition in GH deficient children have not often been studied in a prospective fashion. One such study[1] of a mixed population of GH deficient children with increased fat mass, markedly reduced lean body mass, and some decline in total bone mineral content at baseline indicated that there was a statistically significant reduction in fat mass and an increase in lean body mass after 6 months of GH therapy and a significant improvement in bone mineral content after 12 months of treatment. Favorable changes in body composition continued with increasing duration of therapy, as did improvement in the lipid profiles, which were abnormal at baseline.

Another study of 65 prepubertal children receiving GH and 35 individuals who had completed GH therapy 6 months earlier found that treatment was associated with a remarkable decline in body fat.[2] The girls studied demonstrated a normal age-related increase in fat mass over time, but the boys retained the reduction in the percentage of body fat. However, when GH was discontinued, the return of abnormal body composition was more pronounced in boys than in girls, as was the return of abnormal cholesterol profiles.

Prader-Willi Syndrome. The value of GH therapy to correct abnormalities of body composition that are separate from the issue of height in children is well illustrated in Prader-Willi syndrome, an inherited functional deletion of chromosome 15 that affects approximately 1 in 15,000 children. The syndrome is characterized by obesity, hyperphagia, hypotonia, hypogonadism, hypothalamic dysfunction, and short stature, although the latter is not as severe as that seen in individuals with GH deficiency.

Controversy exists about whether children with the syndrome are truly GH deficient. It is very difficult to test those children for hormone deficiency because their obesity suppresses GH production. However, increasing evidence indicates that those children are GH deficient, because they stop growing when they are placed on a calorically restricted weight reduction diet. Apparently, overnourish-

ment is required for growth in such children.

In a study of 54 children with Prader-Willi syndrome, Carrel and associates evaluated the effects of GH treatment on body composition, strength and agility, and respiratory muscle strength. Their 24-month follow-up results indicate significant increases in linear growth rates, lean body mass, and bone mineral density; a decrease in fat mass; improved agility and physical functioning; and no progression of scoliosis or glucose intolerance.[3]

For such children and their parents, the value of GH therapy is not in the increase in height but rather in improved physical function and ability to do things that could not be done before treatment, such as play half a game of soccer, climb on the school bus unassisted, or ride a bike. From an ethical point of view, it is the responsiveness to GH therapy and the improved functional outcome that should determine entitlement to treatment not the diagnosis of GH deficiency.

GH Dose, Height Outcomes, and Follow Up

Before 1985, the adult height of children with GH deficiency who were treated with pituitary GH ranged from -4.7 to -2.0 SD. Since 1985, when recombinant GH became available, the adult height of children treated with recombinant GH has ranged from -1.5 to -0.7 SD. The marked improvement in adult height has been attributed to higher doses of recombinant GH (2 to 3 times higher than those used with pituitary GH), standardization of dose by weight, earlier chronologic and bone age at the start of treatment, longer duration of therapy, correction of height deficit before the onset of puberty, the frequency of hormone administration, parental heights, gender, and compliance with therapy.

The GH dose and the duration of therapy are critical to favorable height outcomes. When GH deficient children were treated with pituitary GH, they were often given a fixed dose of 2 units, regardless of body size. Now, children treated with recombinant GH are given a higher dose that is standardized to weight: 0.2 to 0.3 mg/kg/wk. A comparison of the efficacy of 3 doses of GH (0.025 mg/kg/d, 0.05 mg/kg/d, and 0.1 mg/kg/d in prepubertal children) found that the 2 higher doses resulted in height SD gains of approximately 1.3 at 12 months and almost 2 at 24 months. In contrast, the 0.025 mg/kg/d dose increased height SD 0.7 and 1.3, respectively.[4]

Other studies in which the effect of GH dose on adult height outcome was evaluated also indicated that a higher dose was more effective. The adult height of participants of a Genentech core study using 0.3 mg/kg/wk was compared to the height outcome from the Kabi International Growth Study (KIGS) in which a mean dose of 0.19 mg/kg/wk was used. The final height was 171.6 cm in the core study versus 166.0 cm in KIGS for men and 158.5 cm versus 154.9 cm, respectively, for women.[5,6]

The duration of GH therapy also has a considerable effect on adult height outcomes. In 3 studies,[5,7,8] the GH dose was constant (0.3 mg/kg/wk) and starting height SDs were similar. The best height outcomes were observed in the children treated for the longest period: 6.4 years in the Genentech clinical trials, 4.6 years in the National Cooperative Growth Study (NCGS), and 3.8 years in the Buffalo study. Mean final heights and gains in height SD for men were 171.6 cm (+ 2.3 SD) in the Genentech trials, 168 cm (+ 1.3 SD) in NCGS, and 166 cm (+1.3 SD) in the Buffalo study.

The frequency of GH administration is another factor that affects final height outcome. A 3-year study involving 65 prepubertal children who

were GH deficient on provocative testing found that daily administration of GH resulted in greater height SD gains at the end of 3 years than did thrice-weekly administration of the same dose (0.3 mg/kg/wk). Over 3 years, there was an extra gain of 1 height SD (or 6.4 cm) with daily treatment.[9] Neither bone maturation nor the onset of puberty was accelerated by daily administration in comparison with thrice-weekly administration.

A review of data from the Genentech trials, KIGS, the Buffalo study, and NCGS revealed that doses of 0.3 mg/kg/wk have no adverse effects on bone age or the age of onset of puberty.[10] However, in all 4 studies, the height gain during puberty was less for females (15 to 19.4 cm) than for males, and less for males (22 to 24 cm) than for healthy, normally growing children (27 to 30 cm).

A recent study in which a higher dose of GH (0.7 mg/kg/wk) was used during puberty reported greater height gain and growth velocity.[11] However, given the cost of GH, it is expected that use of the higher dose would be restricted to use in children who begin treatment late or whose pubertal growth is suboptimal when standard dosing of GH is administered.

Payer's Perspective on Diagnosis and Treatment of Pediatric GH Deficiency

Clinicians who submit a request for coverage of GH therapy to treat children with short stature usually have little idea of how those requests are processed by payers. In addition, review policies regarding GH therapy vary from payer to payer. The initial payer response is a review that is usually performed by a nurse or a physician. Some insurance companies have a nurse or physician, who has minimal experience with the diagnosis of GH deficiency in children, reviewing the request for GH coverage.

In general, insurance companies prefer concrete policies, and they should have guidelines for the approval of GH therapy that have been drafted by endocrinologists. The guidelines should be specific enough to provide direction but flexible enough to permit case-by-case determinations. Insurance companies also tend to respond favorably to requests that involve uses of GH that are approved by the Food and Drug Administration (FDA). However, many insurance companies have their own policy exclusion criteria that are independent of FDA approval, which is their legal right.

Insurance companies also have the right to gather medical information, which is essentially the same information that clinicians need to make their own determination of medical necessity. The patient's growth chart and medical history, including laboratory test results such as scores from provocative tests, are necessary data. Information on the height of the patient's parents should be provided to the payer if that is a factor in the clinician's decision to prescribe GH.[12]

In many instances, requests for coverage of GH therapy are incomplete, and important data are missing. Often, the growth chart is missing or is unreadable because of fax distortion that "blacks out" the grid, particularly that portion below the 5th percentile and above the 95th percentile. Clinicians should be aware of this and be especially careful when submitting growth charts by fax.

Other issues that warrant consideration are the minimal and maximal GH dosage, the duration of therapy, new scientific breakthroughs that suggest the benefits of GH therapy but that have not yet been approved by the FDA, and the extent of a new company's obligation to continue payment for GH therapy when the insured or the insured's parent switches insurance companies.

Turner Syndrome

Turner syndrome is a common chromosomal abnormality (45,X0 karyotype) that occurs once in every 2000 to 5000 live-born phenotypic females. The cardinal clinical features are short stature and infertility, both of which are seen in virtually all patients.

Growth in such individuals is already subnormal in infancy and early childhood, and there is no pubertal growth spurt. Because growth velocity declines early on, many affected girls are significantly below the 5th percentile for height, even at the age of 2, 3, or 4 years. Because patients with Turner syndrome are not GH deficient, GH stimulation testing is not needed in the United States to establish the need for GH therapy as it is in other countries, unless growth is clearly abnormal when compared with that expected for patients with the syndrome.

In 1995, GH at a pharmacologic dose of 0.375 mg/kg/wk was approved in the United States for the treatment of short stature associated with Turner syndrome. With this dose, which is 25% higher than the conventional doses used to treat GH deficiency, many patients can achieve a final height of 60 inches, or 152.4 cm.[13]

Unfortunately, as reflected in the NCGS, early recruitment for this treatment is lagging; ascertainment and enrollment peak in patients who range in age from 10 to 12 years.[14] Treatment is thus initiated late because it does not allow enough time for GH therapy to help such patients achieve a height of 60 inches. In addition, the growth rate for patients receiving therapy for Turner syndrome is not as sustained as with therapy for other indications, although the growth rates for the first year of treatment are comparable. After the first year of treatment, the increase in growth rate in those with Turner syndrome begins to decline, which translates into a less impressive gain in height SD.

A study by Rosenfeld and associates found that combination therapy with 0.375 mg/kg/wk of GH and 0.625 mg/kg/d of oxandrolone resulted in a more robust height gain than did treatment with GH alone (152.1 ± 5.9 cm (mean ± SD) versus 150.4 ± 5.5).[13]

A major issue in the treatment of Turner syndrome is determining when to introduce estrogen therapy. Clearly, it is not beneficial to introduce estrogen too early because it will advance bone age faster than chronological age and impact negatively on final height. Results are better when GH is given early and estrogen administration is delayed until the patient is 15 years of age.[15]

In summary, the appropriate clinical management of Turner syndrome consists of the early administration of GH to enable the child to reach a more acceptable adult height earlier and to allow earlier introduction of estrogen at 12 to 13 years of age if the height deficit is no longer substantial. Combination therapy with GH and an anabolic agent such as oxandrolone could be tried if the patient is 10 to 12 years old and still has a considerable height deficit. Baseline measurements of follicle-stimulating hormone and luteinizing hormone provide some clues about whether spontaneous puberty will occur. If those levels are markedly elevated, spontaneous puberty is unlikely to occur, and anabolic agents can be used with greater confidence.

Cumulative height changes seen in the NCGS, in which the duration of treatment ranged from 1.8 years to 5.6 years, clearly demonstrate that longer treatment with GH translates into greater height gain.[13] Recent data from a long-term Dutch study in which GH doses between 0.46 and 0.63 mg/kg/wk were injected daily for 7 years show that those high doses and the longer duration of treatment result in final heights of 159.1 cm to

167.2 cm, and that the highest dose used produced the greatest final height.[16] The height gains observed in the study by Rosenfeld and associates were not as robust as those seen in the Dutch study (probably because in the latter trial higher GH doses were used). However, gains in height were more robust than those seen in the NCGS because of the longer duration of treatment in the study by Rosenfeld and associates (7.6 ± 2.2 years for patients receiving GH only and 6.1 ± 1.9 years for those receiving GH plus oxandrolone).

Insurance coverage for treatment is likely to be approved easily if on the statement of medical necessity the clinician includes the patient's karyotype and a notation that an open growth plate has been identified. Some payers explicitly exempt treatment with biologicals, which include GH at low and high doses, from coverage. However, because many patients with Turner syndrome are diagnosed late and would therefore benefit from treatment with higher doses of GH, payers should allow flexible dosing in individual cases. Because Turner syndrome requires years of treatment, payers should also grant approval for treatment with GH for periods of at least 1 year and should not require that an entire set of clinical data be submitted every 6 months.

Chronic Renal Insufficiency

Chronic renal insufficiency (CRI) is characterized by an insidious and irreversible loss of nephron function and glomerular filtration that progresses to chronic renal failure and end-stage renal disease (ESRD), which necessitates dialysis and/or renal transplantation. There are no accurate data on the prevalence of CRI in the pediatric population, but it is estimated to be much higher than the 4000 to 4500 cases of ESRD in children.

There are 3 major causes of CRI:

- Structural, which is usually due to maldevelopment of the urinary tract as a result of a congenital defect, as in cases of obstructive uropathy
- Metabolic, such as cystinosis or oxalosis
- Acquired, which is usually the result of an infectious process such as glomerulonephritis, which then progresses to glomerulosclerosis

Growth failure is one of the most common clinical features of CRI, and stunted growth is already apparent in many children at the time of presentation. In fact, the younger the age at the onset of CRI, the greater the degree of growth failure. Most children with CRI do not attain their genetic height potential (indeed, their mean adult height is 2 SD below the norm) because of a combination of factors, including poor growth, delayed puberty that delays and blunts the growth spurt, malnutrition, acidosis, and renal osteodystrophy. Some studies have suggested that parathyroid hormone levels play the major role in determining whether a child with CRI will grow normally, but data are not conclusive.[17]

The effect of malnutrition on growth in children with CRI deserves further mention. Often, these children cannot consume enough calories to sustain their catabolic state or grow normally. Although they may grow normally and may maintain a normal growth rate when their nutritional status has been optimized and other supportive measures have been instituted, they do not experience catch-up growth and may not regain the height they have lost. If those children are to be treated with GH, their nutritional and medical status must be optimized to ensure an adequate response to therapy.

Three mechanisms in the GH-IGF axis have been implicated in the

poor growth seen in children with CRI:

- A possible decrease in the number of GH receptors, which reflects a decrease in GH-binding protein activity in the serum
- Reduced secretion of IGF-1
- An increase in IGFBP-3, which causes a decrease in the bioavailability of free, biologically active IGF-1

Although it had been thought that correction of the renal status by dialysis or transplantation would normalize growth in such patients, the results of studies assessing these treatments have been disappointing. In a study of 51 patients undergoing dialysis, one third achieved normal growth, one third exhibited retarded growth, and one third experienced severely retarded growth. Normal, retarded, and severely retarded growth are defined as loss of length for age less than .2 SDs/year of therapy; approximately .39 SDs/year of therapy; and greater than .5 SDs/year of therapy, respectively.[18] Another study indicated no improvement in growth after continuous ambulatory peritoneal dialysis.[19] Similarly, a study of children who had undergone renal transplantation up to 3 years earlier found no evidence of catch-up growth; their height was maintained at -2 SD despite normalization of growth rate posttransplant.[20]

Promising study results of GH treatment of uremic animals in the early 1980s prompted successful clinical trials in children, which ultimately led to FDA approval of treatment with GH before transplantation in those with CRI. In one study, control patients had low-normal IGF-1 levels, and those treated with GH (somatropin, in this study) had an improvement in IGF-1 levels. At the end of the first year of the study, the growth rate was 6.5 cm/yr in the 28 control patients compared with 10.8 cm/yr in those who received GH. At the end of the second year, the growth rate was 5.5 cm/yr in the control subjects and 7.8 cm/yr in the treated patients. When therapy was changed from placebo to GH, there was a dramatic improvement in height SD scores from the pretherapy score of -2.9 SD to –1.9 SD. GH treatment did not accelerate bone age or the progression to ESRD.[21]

In summary, treatment with somatropin in this study corrects height deficit in most children with CRI before transplant and significantly improves the mean growth rates and height SD; 65% of treated patients achieve heights in the normal range after 2 years and 91% achieve normal-range heights after 3 or more years of such therapy.[21]

Several key issues remain regarding CRI in children:

- What are the absolute growth criteria for the initiation of GH therapy pretransplant?
- How soon should GH therapy be initiated and for how long?
- Should managed care companies facilitate optimal medical management before approving GH treatment?

Idiopathic Short Stature

Idiopathic short stature syndrome is defined as significantly short stature (greater than -2.5 SD); persistently low growth rate; and no evidence of systemic disease, malnutrition, hypothyroidism, chromosomal abnormality, or classical GH deficiency on provocative testing. There are multiple causes of that syndrome, including genetic short stature, familial short stature, constitutional delay of puberty, a variety of GH axis dysfunctions (notably, IGF deficiency), partial GH insensitivity syndrome, combinations of constitutional delay and genetic short stature, and causes of unknown origin.

Dozens of studies reported in the literature have shown that children

who have been classified as having idiopathic short stature will have a short-term increase in growth rate when given GH. Long-term studies, most of which were conducted on small numbers of patients, have reported height gains ranging from none to about 7.5 cm. Some of the larger studies, however, have shown the most benefit from treatment with GH.

In a recently reported study, 121 children with idiopathic short stature syndrome who were prepubertal (mean age, 10 years) at study entry were treated for 2 to 9 years with GH at a dose of 0.3 mg/kg/wk.[22] In an attempt to avoid confounding effects of puberty, at least for the first few years of the study, the investigators recruited girls with a bone age of less than 9 years and boys with a bone age of less than 10 years. Bone age was determined by the Fels method, and predicted adult height was determined by Bayley-Pinneau tables.

Eighty of the study subjects achieved more than 98% of their final height; the bone age was more than 16 years for males and more than 14 years for females. The final height was 165.5 cm ± 7.2 cm for the 57 males and 153.1 cm ± 4.8 cm for the 23 females, which was halfway between predicted height and midparental target height for those subjects, for a gain over predicted height of 5 cm in males and 5.9 cm in females. Overall, 50.9% of the males and 60.8% of the females reached or exceeded their predicted height.[22]

The study findings indicate that GH treatment increases mean final height in those with idiopathic short stature and that the mean final height is significantly greater than that of equally short untreated controls. Two mechanisms may produce the beneficial effects:

- GH therapy corrects a defect in GH secretion or action (21% of the study subjects had low baseline levels of GH-binding proteins, and 2 subjects had a heterozygous defect in the extracellular GH-binding region of the GH receptor gene, which suggests partial GH sensitivity; an additional 11% had a low baseline level of IGF-1).
- GH treatment exerts a pharmacologic effect on growth.[22]

The results of the study described above and new data from studies conducted in England and Germany indicate that GH treatment has a beneficial effect on adult height in individuals with idiopathic short stature. As a group, children with idiopathic short stature are just as short as and grow just as slowly as do children with GH deficiency. The reason for this is not fully known. One third of the children in the study described above had evidence of a disorder of the GH-IGF axis.[22]

GH treatment could be considered for children with idiopathic short stature who exhibit a significant height deficiency (-2.5 SD [instead of -2 SD] when compared with that of appropriate controls), a persistently low growth rate (less than 25% observed over a period of at least 1 year or less than 40% over 2 years), and no evidence of systemic disease.

Deciding Coverage for GH Treatment

The need for mutual understanding among payers and providers regarding authorization for insurance coverage for GH treatment has never been more urgent. To deal with requests from clinicians to cover GH treatment, payers have developed a spectrum of policy and implementation plans to guide decisions regarding coverage.

One such policy and implementation plan was developed in 1991 by the New England-based Harvard Pilgrim Health Plan. Under the plan, the GH review committee is chaired by a pediatric endocrinologist and consists of a medical director, a nurse practitioner/case manager, a pharma-

cy director, and an administrative assistant/analyst.

When the policy was first implemented, the committee approved GH therapy for the treatment of GH deficiency and Turner syndrome. In 1996, they approved therapy for CRI prior to transplantation in patients whose renal failure and nutritional status were managed optimally. The committee added criteria for wasting caused by the acquired immune deficiency syndrome (AIDS) in adults in 1997, criteria for GH deficiency in adults in 1998, and pediatric-to-adult transition criteria (growth velocity less than 2 cm/yr and fused epiphyseal plates) in 1999.

When committee members developed guidelines for the coverage of GH treatment, they considered several factors, including safety, efficacy, cost, ethics, and the results of endocrine studies.

Approval for coverage is usually granted in 2 or 3 days for those with GH deficiency or Turner syndrome and for patients with CRI who are to undergo transplantation as long as the application meets coverage criteria.

Applications for coverage of GH therapy in cases in which the criteria for therapy are not clear require more time to process because of consultations with experts, surveys, and initial and secondary reviewing of the literature.

Another key feature of the policy and implementation plan is the rolling review process, which is performed every 6 months to determine whether treatment endpoints are being achieved and the therapy is appropriate for the patient.

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