

Growth Hormone Use in Transitioning Patients—Clinician and Payer Concerns

Based on presentations by Stephen LaFranchi, MD; Margaret H. MacGillivray, MD; and Pete Fullerton, PhD

Presentation Summary

Determining which patients with childhood-onset growth hormone (GH) deficiency will require continuing GH therapy into and/or throughout adulthood raises clinical and economic issues, such as retesting, appropriate dosing, and the risks and benefits of uninterrupted GH treatment versus the discontinuation of therapy.

In his review of the evaluation and management of patients transitioning from GH therapy in childhood to GH therapy in adulthood, Dr. Stephen LaFranchi

focuses on the odds of having ongoing GH deficiency, the changes that occur when therapy is discontinued, appropriate follow up of patients who discontinue treatment, and issues regarding the reinitiation of therapy. Dr. Margaret H. MacGillivray addresses appropriate monitoring and follow up of patients in transition, as well as their classification by etiology and severity of GH deficiency. Dr. Pete Fullerton explores new issues regarding GH deficiency treatment from a managed care perspective.

Payer Highlights

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- Managed care plans and pharmaceutical companies can join forces to provide needed data for the payer review process for coverage of GH therapy.
- More payers are applying a clinical evidence-based approach to reviewing requests for coverage for expanded indications, new drugs, and formulations.
- Managed care plans are requesting pharmacoeconomic outcomes modeling to be used in the reimbursement review process.

The term “transitioning” refers to adolescents with childhood-onset growth hormone (GH) deficiency who have been treated with GH and are now approaching the completion of therapy for height indications; that is, they have achieved adult or near-adult height, which is commonly defined as a growth rate of less than 2.5 cm/yr and a bone age of greater than 17 years in boys and greater than 14 years in girls. However, although those adolescents are approaching adult height, they have not necessarily attained adult bone mass and body composition. Determining which of those adolescents will require ongoing GH therapy raises a number of clinical and economic issues, many of which are addressed in this article.

Rationale and Diagnosis in Transitioning Patients

Transitioning patients usually range in age from 15 to 18 years of age, and occasionally they are as old as 20 years of age. Two major clinical issues in the management of those patients are determining whether an ongoing GH deficiency exists and will require treatment and recommending the continuation or interruption of GH therapy. If a patient elects to discontinue therapy, issues of importance revolve around the need for monitoring and the possibility that GH therapy will have to be reinstated.

The odds that a transitioning patient will exhibit ongoing GH deficiency vary according to the etiology of the deficiency and from study to study. For example, depending on the study, between 25% and 75% of transitioning patients with isolated idiopathic GH deficiency exhibit normal values (above 5 ng/mL) on provocative retesting. In contrast, most patients with GH deficiency with or without other pituitary hormone deficiencies associated with known congenital syndromes (eg, septo-optic dysplasia), hypothalamic-pituitary

tumors, or other acquired causes of hypopituitarism will retest as having ongoing GH deficiency, as will virtually all transitioning patients with multiple pituitary hormone deficiencies.

Retesting patients with isolated idiopathic GH deficiency may include an insulin tolerance test, an arginine stimulation test, or arginine plus GH-releasing hormone testing. A low insulin-like growth factor 1 (IGF-1) level (and possibly IGF-binding protein-3 test) is sufficient for retesting patients with multiple pituitary hormone deficiencies or GH deficiency associated with con-

Table 1. Risks Versus Benefits of GH Therapy: Uninterrupted Versus Discontinuation

Parameter	Uninterrupted Treatment	Discontinuation of Treatment
Body composition		
Percent fat	No increase	Abnormal increase
Lean body mass	No decrease	Abnormal decrease
Physical strength	Normal	Reduced
Exercise tolerance	Normal	Reduced
Bone mass		
	Reach peak (adult) mass	Reduced bone mineral density
Risk of osteoporosis, fractures	Normal	Increased
Lipid profile/cardiovascular risk		
Cholesterol, triglycerides	Normal	Increased
Cardiovascular-related morbidity and mortality	Normal	Increased
Quality of life		
Psychological impact	Positive	Negative
Educational impact	Positive	Negative
Vocational impact	Positive	Negative

GH = Growth hormone.

genital syndromes, hypothalamic-pituitary tumors, or other acquired causes of hypopituitarism.

After retesting has confirmed the presence of ongoing GH deficiency, further management—uninterrupted GH therapy versus discontinuation of treatment—must be discussed with the patient and his or her parents.

Uninterrupted therapy continues to provide the favorable nongrowth effects of GH on body composition, bone mineral density, lipid profiles, cardiovascular risk, and quality of life (Table 1). However, some patients choose to discontinue therapy, at least temporarily, because they have reached their adult height and would now prefer to “take a break” from daily GH injections.

At present, few data and no controlled trials specifically address bone mineral density and body composition in transitioning patients. Therefore, much of what is known in this regard is based on extrapolations from data in adults who have continued or discontinued GH therapy.

One of the few studies of patients in transition involved 16 male patients who ranged in age from 16 to 19 years. Study results indicated that unfavorable changes in body composition occur as early as 6 to 12 weeks after the discontinuation of GH therapy in those with ongoing GH deficiency.¹ In that study, dual-energy X-ray absorptiometry (DEXA) scans for body composition and bone density were performed immediately after treatment was discontinued and 6 and 12 weeks later. Over that short period of time, the 6 boys who retested as GH deficient exhibited an increase in body fat from 10 to 14 kg (15% to 20%) and a decrease in lean body mass from 42 to 38 kg, but similar changes were not observed in the 10 boys who retested as normal.

An Italian study² of 11 patients (mean age, 25 years) who discontinued and then restarted GH ther-

apy demonstrated that exercise tolerance and cardiac output decreased soon after therapy was discontinued and improved after it was reinitiated. A small British study³ of 5 patients in whom GH deficiency developed during puberty indicated that lumbar bone mineral density significantly decreased when no GH therapy was given but increased to normal when therapy was administered.

Few data on transitioning patients address cardiovascular risk, but extrapolation from studies in adults suggests that the discontinuation of GH therapy increases cholesterol levels and the risk for cardiovascular morbidity and mortality. A large multinational European study⁴ of childhood-onset and adult-onset GH deficiency found that the ratio of high-density lipoprotein (HDL) to low-density lipoprotein (LDL) improved in both patient groups during 18 months of GH therapy. The higher the ratio, the more favorable the reduction in cardiovascular risk.

Quality-of-life factors have not been studied in transitioning patients. However, when compared with “normal” same-age peers, children and adolescents with GH deficiency have a poor outlook psychosocially, educationally, and vocationally. They are older when they date and marry, if they marry at all; they do not go as far in school; and they tend to hold lower-level jobs and earn lower salaries than do normal same-age peers.^{5,6} Theoretically, treatment with uninterrupted GH therapy should improve that disparity.

For patients who elect to discontinue GH therapy, the following assessments are recommended to determine whether ongoing GH deficiency exists and to identify the need for reinstatement of therapy:

- Physical examination (eg, weight, waist-to-hip circumference, skin-

fold thickness measurements at selected sites)

- Biochemical tests (eg, IGF-1, lipoproteins, markers of bone formation such as osteocalcin and alkaline phosphatase levels, and markers of bone resorption such as N-telopeptide levels)
- DEXA scans to determine bone mineral density and body composition
- Measurements of physical strength and exercise tolerance
- An echocardiogram

After the diagnosis of GH deficiency has been reconfirmed, GH therapy is recommended to preserve normal physiology. Preventing untoward physiologic changes via this approach is preferable and is ultimately less expensive than correcting those problems after they have developed.

Treatment of Transitioning Patients With Childhood-Onset GH Deficiency

Patients with childhood-onset GH deficiency are a more heterogeneous population than are those with adult-onset GH deficiency because some of the former group will require continuation with GH therapy. It is the responsibility of the clinician to make that determination.

Classifying patients by etiology and severity of their GH deficiency is the first step in an evaluation. Patients with organic disease and magnetic resonance imaging (MRI)-documented abnormalities in the hypothalamus or pituitary, those with multiple pituitary hormone defects, and those with congenital GH deficiency are most likely to require ongoing therapy as adults. Children with severe GH deficiency at initial diagnosis (ie, peak GH levels less than 5 ng/mL after the first provocative test) are at risk for permanent lifelong GH deficiency. Those patients probably should continue therapy indefinitely until it can be established that “rest periods”

from therapy are safe, because adverse metabolic changes could develop if therapy is discontinued. The care plan for those patients is outlined in Table 2.

Another challenge is the management of children with isolated idio-

Table 2. Theoretical Care Plan for Patients in Transition

If patient exhibits:	
	Growth rate < 2.5 cm/yr
	Bone age > 14 yrs in girls, >16 to 17 yrs in boys
Classify patient:	
	Idiopathic versus organic (as determined by MRI)
	Congenital versus acquired
	Isolated versus multiple
	Severe versus less severe
Retest patient:	
	Insulin tolerance test ± other stimulation tests
	IGF-1 levels, body mass index, bone mineral density, body composition
	Lipids, quality of life, etc.
Retest peak GH level: < 5 ng/mL	
Treatment	GH 0.006 to 0.025 mg/kg/wk
Follow up	Weight, height, body mass index, etc. IGF-1 levels Lipids Quality of life/strength, stamina Bone mineral density/body composition every 1-2 yrs
Duration of treatment	Continuous or intermittent?
Retest peak GH level: >5 ng/mL	
Treatment	No treatment unless problems arise
Follow up	Annual evaluation Bone mineral density/body composition every 2-5 yrs

GH = Growth hormone; IGF-1 = insulin-like growth factor 1; MRI = magnetic resonance imaging.

pathic GH deficiency, who usually will not require ongoing therapy. In most cases, therapy is discontinued in this group primarily because of patient and parent satisfaction with the final height achieved. After therapy has been discontinued, however, careful follow up is essential.

More data are needed on the management of therapy in patients who require ongoing therapy. Should treatment be continuous or intermittent? Can such patients take a "drug holiday" and if so, how often and for how long? Which dose should be used? Currently, doses of 12.5 to 25 $\mu\text{g}/\text{kg}/\text{day}$ are used in nonobese young adults with childhood onset of GH deficiency. However, some endocrinologists have reduced the dose to 2 to 6 $\mu\text{g}/\text{kg}/\text{day}$ in patients with craniopharyngioma; the dose is based on ideal body weight rather than on actual weight. Another approach is to use a dose that is not based on weight.

More data are also needed on the intensity of follow up of patients who do not require ongoing GH therapy (ie, those with isolated idiopathic GH deficiency). There is no consensus on this issue. Although bone mineral density and body composition determinations are now suggested every 2 to 5 years (Table 2), this may not be the optimal interval.

One approach to those issues is to use healthcare dollars to conduct research that would yield valuable information about which transitional patients are at risk for problems related to abnormal body composition, reduced bone mineral density, abnormal lipids, and cardiovascular morbidity.

Evaluating Coverage of GH in Transitioning Patients

The evaluation of expanded clinical indications for the treatment of GH deficiency and new dosage forms are current issues of interest to payers.

To facilitate these evaluations, Regence Blue Shield, part of a 4-state Blue Cross/Blue Shield plan in the Pacific Northwest, adopted a clinical evidence-based approach to review the efficacy and safety of expanded indications, new drugs, and drug formulations.⁷

An important step when evaluating injectables, such as GH, is to gather data that conform to the Blue Cross/Blue Shield technology assessment criteria. "Technology" refers to either a drug or a dosage form. The criteria are as follows:

- The technology must have final approval from the appropriate governmental regulatory body (although this is not applicable for an expanded indication).
- Scientific studies must permit conclusions about the effect on health outcomes and must improve net health outcomes.
- Clinical data must indicate that the drug or treatment is as beneficial as are established alternatives.
- Clinical results must be attainable outside the investigational drug setting in a tertiary care center.

The Regence Blue Shield approach requires that drug manufacturers submit all published and unpublished studies evaluating a drug for an expanded indication or a new dosage form. The studies must be submitted in a standard format that includes a description of the diseases and a description of the therapeutic role of the drug, particularly with respect to its clinical efficacy and safety. This standardized process permits a comprehensive, evidence-based evaluation of clinical and economic data.

Regence Blue Shield takes the process one step further by requiring pharmacoeconomic outcomes modeling. It was the first major health plan in the United States to require such modeling for expanded indications and new drug forms for use in evaluating the clinical value of the drug (ie,

the outcomes that have an impact on health). The use of GH in the transitioning patient is an example of a significant expanded indication. Such modeling clarifies available pharmacoeconomic data and explains their clinical relevance.

The Regence Blue Shield approach permits a manufacturer to use appropriate endpoints for evaluating its product and the therapy for which the product is intended but requires clarification of the assumptions and statistical biases of each study.⁸ This creates a theoretical picture of the condition or disease. Regence Blue Shield requires that it insert its own data into the manufacturer's model to obtain a more pragmatic picture.

In essence, Regence Blue Shield reviewers consider the pharmacoeconomic outcomes model, add appropriate data from published studies in which GH therapy was terminated, and then extrapolate from other data in the literature to determine the impact of changes in bone density and lipid profiles on costs. Such extrapolations are necessary because long-term data are not available when pharmaceutical companies apply to the FDA for expanded indications or a new dosage form. Although surrogate markers are not as good as solid outcome markers, they do permit a managed care organization to define issues of clinical value to its members and to determine which health outcomes render a drug a valuable addition to its formulary. This is the type of information needed in managed care decision making about coverage for GH treatment in the transitioning patient.

Because the modeled pharmacoeconomic outcomes vary according to the product and its indications, the Regence Blue Shield approach permits the manufacturer to design modeling that is appropriate for its product and indication. However, some endpoints are more meaningful to a managed care plan. For example,

indirect cost savings accruing from the increased economic productivity of the patient on treatment is not as valuable to the healthcare plan as are other measures, such as improved quality of life. In addition, Regence Blue Shield, like most other Blue Cross/Blue Shield plans and other plans across the country, does not rely on FDA approval of a new off-label indication before providing coverage.

Managed care plans need as much data as possible that pertain to expanded coverage for GH therapy for the transitioning patient and new GH dosage forms. Regence Blue Shield looks to the pharmaceutical manufacturer for pharmacoeconomic outcomes modeling and to assemble the appropriate published and unpublished studies. Outcomes data on GH use to treat constitutional growth delay in adult and geriatric patients and for patients in catabolic states are also needed.

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