

Issues Related to Recombinant Human Growth Hormone Utilization and Optimization in a Health Plan Setting

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Burden of Growth Hormone Deficiency in Adults: Body Composition

The effects of growth hormone deficiency (GHD) in adults have been studied with greater intensity over the last 2 decades. An early study demonstrated that male and female patients with hypopituitarism and GHD had a 3-fold greater risk of fractures than control patients despite receiving regular hormonal replacement therapy (excluding growth hormone).¹ Further studies have confirmed that GHD decreases bone mass and that the decrease in bone mass correlates with the severity of GHD.² GHD also causes reduced lean body mass, increased body fat, fatigue, and a reduced ability to perform daily activities.¹⁻⁶ Recently published Endocrine Society guidelines on treating adult GHD recognize the improvements in body composition associated with recombinant human growth hormone (rhGH) therapy in adults.⁷ A 10-year study of rhGH therapy showed that bone mineral density increased progressively with treatment, with greater benefits observed in men. Women without adequate estrogen levels did not benefit to the same extent as men.⁸

Burden of GHD in Adults: Cardiovascular Disease Surrogate Outcomes

Data for 2589 patients with GHD from the Pfizer International Metabolic Database (also known as KIMS) showed that patients with GHD had elevated total and low-density lipoprotein (LDL) cholesterol, increased waist circumference and body mass index (BMI), and increased blood pressure.⁹ The percentage of those with elevated total cholesterol increased with age, and approximately 71% of all patients with GHD had cholesterol levels above 200 mg/dL. Trends for increased LDL-cholesterol and triglyceride levels showed similar increases above normal. After adjusting for BMI, age, and sex, studies have reported a 20% increase in carotid intima-medial thickness in adults with GHD compared with normal adults.⁶ Leonsson and colleagues examined the inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6) and found that patients with GHD showed a 2-fold increase in IL-6 compared with matched controls. CRP was also elevated compared with non-obese patients, but was similar to controls when corrected for BMI.⁴ The cumulative elevation of CVD risk factors suggested an increased risk for CVD; however, controlled trials

Abstract

Healthcare expenditures in the United States are high and continue to increase; as a result, providers and managed care organizations have to evaluate the impact of specialty drugs such as recombinant human growth hormone (rhGH) therapy. As the number of approved indications for rhGH therapy has increased, so too have questions about the appropriate allocation of resources for such therapy. This is particularly true for the recent rhGH indications in children with idiopathic short stature and those short for gestational age who fail to attain normal growth percentiles. With a large increase in the number of children eligible for rhGH therapy, questions arise as to whether all eligible children should be treated with rhGH, and what are the appropriate length of treatment and optimal treatment outcomes. These are important questions for managed care organizations who must determine the treatment parameters that produce the best outcomes in children. The primary disease burdens of growth hormone deficiency (GHD) in adults are the changes in body composition and metabolic parameters, and reduced quality of life, all of which are associated with improvements following rhGH therapy. In adults, the primary economic burden of GHD is healthcare-related costs such as increased hospital days and clinic visits.

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Table. Healthcare Costs and QOL Improvements With rhGH Therapy in Adults With GHD¹⁷

| | Baseline | 12 Months |
|---|----------|-------------------|
| Sick leave days (number in previous 6 months) | 9.5 | 3.8 ^a |
| Hospital days (number in previous 6 months) | 1.7 | 0.6 ^a |
| Doctor visits (number in previous 6 months) | 2.1 | 1.4 ^b |
| Leisure time physical activity (visual analog scale score) | 40.8 | 51.1 ^c |
| Satisfaction with leisure time activities (visual analog scale score) | 41.6 | 48.8 ^c |
| Need for assistance with daily activities (%) | 21 | 16 ^a |

^a*P* < .05 vs baseline.
^b*P* < .01 vs baseline.
^c*P* < .001 vs baseline.
 GHD indicates growth hormone deficiency; QOL, quality of life; rhGH, recombinant human growth hormone.
 Adapted from Hernberg-Ståhl E, Luger A, Abs R, et al. *J Clin Endocrinol Metab.* 2001;86:5277-5281.

specifically analyzing cardiovascular end points are required to further elucidate the risk associated with GHD in adults. Many studies have shown that CVD risk factors improved with rhGH therapy, including improved total cholesterol levels, a trend toward improved LDL cholesterol levels, and a reduction in blood pressure.⁹⁻¹¹ Reports on surrogate CVD end points with rhGH therapy are encouraging; however, long-term controlled trials are required to confirm these results.

Quality of Life and Economic Burden: Improvement With rhGH Therapy

Quality of Life (QOL) is significantly reduced in adults with GHD compared with the general population.¹²⁻¹⁴ Although there is variability among studies assessing the effects of GHD on QOL, a recent review of studies suggests that the type of tools used to measure QOL may affect outcomes. Generic tools, such as the Nottingham Health Profile or the Psychological General Well Being Scale, tend to show less robust results compared with disease-specific tools such as the Questions on Life Satisfaction-Hypopituitarism and the Adult Growth Hormone Deficiency Assessment questionnaire.¹⁵ Not only do the disease-specific tools show an increased effect of the disease on QOL at baseline, they generally show a greater improvement in QOL after treatment with rhGH.

Koltowska-Häggström and colleagues used a database that included patients with GHD from England, Wales, the Netherlands, Spain, and Sweden to study QOL using the disease-specific questionnaire Quality of Life–Assessment of

Growth Hormone Deficiency in Adults (QOL-AGHDA).¹² Those with GHD had much lower QOL-AGHDA scores compared with the general population from each country. Patients with GHD had the lowest scores in QOL dimensions related to memory, concentration, and tiredness, followed by tenseness, self-confidence, and socializing. Long-term rhGH treatment (at least 5 years) tended to normalize the difference in scores between those with and without GHD.¹⁶

The economic burden of GHD has been reported primarily in studies that show an improvement in healthcare-related costs after treatment with rhGH. Patients with GHD report increased sick leave from work and

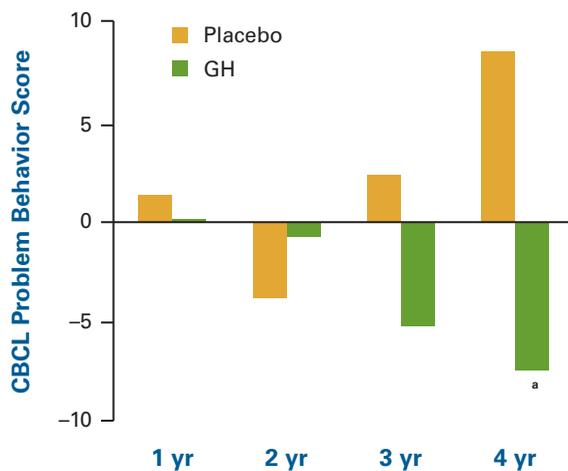
increased healthcare access, including increased hospital days and provider visits, and the need for assistance with daily activities (Table).¹⁷ Using healthcare-related data from KIMS, Hernberg-Ståhl and colleagues showed a high rate of sick leave from work and other healthcare-related costs in patients with GHD. After treatment with rhGH for 12 months, sick leave, hospital days, doctor visits, leisure time, physical activity, satisfaction with physical activity, the need for assistance with daily activities, and QOL (AGHDA scores) significantly improved.

Pediatric Burden of GHD and Other Growth-Related Disorders

The burden of GHD in children is more difficult to evaluate, since there is some debate about disability associated with short stature. However, short stature can have a negative impact on the ability to perform daily activities if an adult height of at least 150 centimeters is not attained. Furthermore, those with other conditions that affect height, such as Prader-Willi syndrome, can be adversely impacted by associated factors, such as increased body fat.¹⁸ As discussed by Rogol in this supplement,¹⁹ the psychosocial burden of short stature is controversial, although many studies show that children of short stature are negatively impacted, especially with respect to behavioral issues.^{20,21}

In a Japanese study by Lee and colleagues of 116 children with idiopathic short stature (ISS) and 127 with GHD, the Child Behavior Checklist (CBCL) was used to assess the psychosocial profiles of children aged 4 to 15 years.²² Children with ISS and GHD had higher CBCL scores compared with

Figure 1. Change in CBCL Problem Behavior Score After 4 Years of rhGH Therapy²⁰



^a*P* < .05 vs control. CBCL indicates Child Behavior Checklist; rhGH, recombinant human growth hormone.

normal children. Subscales that measure QOL also indicated a significant increase in social and attention problems in those with ISS or GHD compared with controls. A placebo-controlled study of 68 children (53 males, 15 females) measured psychosocial differences in treated or untreated children with marked ISS (those with a height at least 2.5 standard deviations below the normal population mean). Patients received rhGH 0.074 mg/kg or placebo (subcutaneously 3 times per week) until their height velocity decreased to less than 1.5 centimeters per year.²⁰ CBCL and Self-Perception Profile scores were within normal range at baseline and no significant differences were observed between

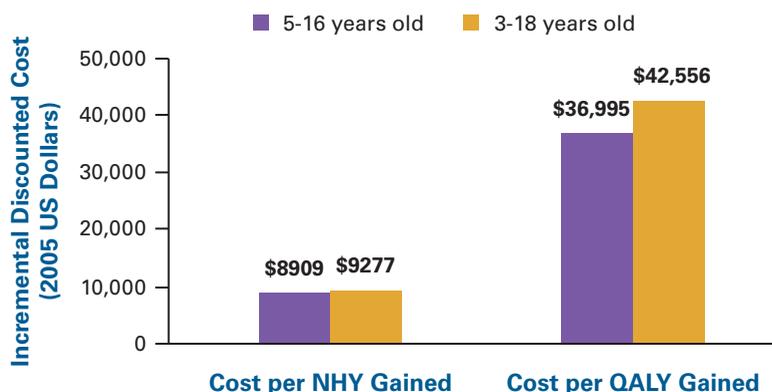
groups during the first 2 years. Thereafter, those given rhGH showed an improvement in CBCL scores for behavior problems compared with those given placebo (Figure 1).²⁰

Cost-Effectiveness of rhGH Therapy in Children

The cost of treating children with rhGH is estimated at \$52,634 per inch (or 2.54 cm).²² Because this is a high-cost treatment, benefits for the patient are an important aspect of justifying the expense for managed care organizations. Only a few long-term studies have evaluated the costs and benefits of rhGH therapy in children with ISS. One study used the Wessex Development and Evaluation Committee report to evaluate quality-adjusted life-years (QALYs). The QALY scale included a disability rating, a physical discomfort scale covering 5 levels of pain, and a distress scale covering 5 levels of emotional distress. The cost-effectiveness and cost utility of treating children aged 5 to 16 years with rhGH was estimated at approximately \$8900 per normal height year gained and \$37,000 per QALY gained, respectively (Figure 2).²³

To maintain the cost-effectiveness of rhGH therapy in ISS, it is important to identify the condition early and start treatment as soon as possible.²² The study by Lee and colleagues showed that earlier age at initiation of rhGH therapy was associated with reduced cost per inch. This is partially because rhGH is dosed by weight; younger children weigh less than older children and therefore require a lower dose of rhGH. Identifying children who will be most responsive to therapy is also critical for maintaining cost-effectiveness of treatment, especially because there is great variability in responsiveness to rhGH treatment among children with ISS. If all eligible children with ISS were treated in the United States, the cost would be substantial.²² With such high costs of treatment, to achieve optimal results, it is important to identify children who will benefit most from treatment and determine the appropriate age for rhGH therapy.

Figure 2. Cost-Effectiveness of Treating Children With rhGH Therapy²³



NHY indicates normal height year; QALY, quality-adjusted life-year; rhGH, recombinant human growth hormone. Reprinted with permission from Joshi AV, Munro V, Russell MW. *Curr Med Res Opin.* 2006; 22:351-357.

In the article by Rogol in this supplement,¹⁹ the criteria for diagnosing GHD and other conditions causing short stature were discussed. However, not all managed care organizations cover ISS, even though it is an FDA-approved indication for rhGH therapy.²⁴⁻²⁶ In addition to meeting the criteria for diagnosis of GHD, some managed care organizations may also require that a patient be followed up to 6 months by a pediatric endocrinologist prior to the initiation of rhGH therapy. If all criteria for diagnosis are maintained, then the patient

can be initiated on rhGH therapy with a follow-up evaluation after 6 months.²⁷ Some managed care organizations require an annual reassessment of growth.²⁵ The dose may be increased during the second 6-month treatment period, but rhGH therapy may be discontinued if the patient does not achieve a growth velocity of at least 4 centimeters per year, or for continued treatment over 1 year, a growth rate at least 50% higher than the previous year. Some managed care organizations may discontinue rhGH therapy if the height increase is less than 3 centimeters per year or if there is evidence of fusion of epiphyses during treatment.²⁶

Case Studies

Presented here are 3 case studies that illustrate the individualized management of rhGH therapy.

Case 1

Jenny is a 6-year-old female. Her parents were referred to an endocrinologist because Jenny's growth rate did not seem normal. It was determined that her height was 3 SDs below the normal population mean. The endocrinology clinical exam and provocation test indicated that she had GHD. Jenny was started on rhGH therapy at a dose of 0.24 mg/kg/week. At the end of 2 years, she attained a height 0.5 SD below the normal population mean. Treatment was continued for 1 more year and then discontinued. Her final adult height was 0.5 SD less than the normal population mean.

Case 2

John is a 7-year-old male with a height 2.25 SDs less than the normal population mean. All provocation tests did not show any evidence of GHD. He was diagnosed with ISS and was initiated on rhGH therapy, which was titrated to a final dose of 0.35 mg/kg/week. At the end of a 6-month trial period, his height was 2.0 SDs less than the normal population mean and 1.8 SDs less than mean after 1 year. Because John was responding to treatment, rhGH therapy was continued for 4 years. John attained an adult height of 1.0 SD less than the normal population mean.

Case 3

Robert is an 8-year-old male with a height 2.8 SDs less than the normal population mean. He was diagnosed with ISS and initiated on rhGH therapy. The rhGH dose was titrated to a final dose of 0.40 mg/kg/week. At the end of the 6-month trial, his height remained 2.8 SDs less than the normal population mean. After conferring with the patient and family, it was determined that adherence was not the reason for lack of response, so treatment was discontinued.

Conclusions

GHD is a healthcare and QOL burden for adults and is associated with increased risk for surrogates for CVD, such as high blood pressure. Therapy with rhGH has been shown to reduce the burden of GHD and improve QOL in adults. Studies evaluating the cost benefit of treating GHD and other conditions that cause short stature in children sug-

gest that rhGH therapy improves the burden of GHD and QALYs. In children with ISS, those receiving rhGH therapy demonstrated fewer behavioral problems than children not receiving rhGH therapy.

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