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Growth Hormone Therapy for Short Stature: Is the Benefit Worth the Burden?

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IN 1985, APPROVAL of recombinant human growth hormone (rhGH) made available a virtually unlimited resource to replace human pituitary-derived GH, which had been withdrawn for safety concerns. During the ensuing 2 decades, clinical trials spearheaded by pediatric endocrinologists and supported primarily by manufacturers of rhGH strived to show that rhGH treatment could improve growth rates and eventual height in children without growth hormone deficiency (GHD) who are short as a result of (sequentially) Turner syndrome (TS), chronic renal insufficiency (CRI), small for gestational age (SGA), Prader-Willi syndrome (PWS), or idiopathic short stature (ISS). Approval of these new indications validated the notion, first proposed in 1990,¹ that if rhGH treatment is effective at increasing height in non-GHD children, then the etiology of short stature is not morally relevant in deciding who is entitled to treatment. These children all share a central and seemingly valid concern: "I am short and I would like to be taller."

The difficulty is that the phrase "like to be taller" in this context ranges in meaning from "physically need to be taller" to "would feel better if I were taller" or "would make my parents feel better if I were taller." The key questions are: Which conditions, if any, lead to a degree of short stature that is sufficiently disabling to warrant medical treatment? If any are sufficiently disabling, what final height should be sought? If height is largely a surrogate outcome for improved quality of life, analysis of therapeutic value of rhGH therapy for short stature requires not only examination of effects on adult height but also of the rationale for intervention itself (ie, presumed disability resulting from short stature), whether improved height actually leads to better psychosocial outcomes, and how benefits compare to risks and costs. As discussed below, recent studies provide information needed to begin this critical appraisal.

HOW MUCH HEIGHT IS ADDED BY GH THERAPY?

TS

Numerous studies demonstrate that rhGH, with or without anabolic steroids, can accelerate growth and lead to height greater than predicted in girls with TS.²⁻⁴ In one cohort, mean height of girls who completed a mean of 7.6 years of rhGH therapy ($n = 17$) was 150.4 cm, a gain of 8.4 cm over the expected average height, whereas those treated with rhGH plus oxandrolone ($n = 43$) achieved a mean final height of 152.1 cm, an average gain of 10.3 cm over predicted height without treatment.² More modest effects on total height gain (eg, mean: 0.7 SD [~ 4.9 -cm

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Key Words

endocrinology, growth hormone treatment, ethics, growth failure, short stature

Abbreviations

GH—growth hormone
rhGH—recombinant human growth hormone
GHD—growth hormone deficiency/deficient
TS—Turner syndrome
CRI—chronic renal insufficiency
SGA—small for gestational age
PWS—Prader-Willi syndrome
ISS—idiopathic short stature
FDA—Food and Drug Administration

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increase³ or 7.2-cm increase⁴) are also reported, particularly when initiation of estrogen treatment occurred before 14 years of age.

CRI

A randomized, double-blind, placebo-controlled study of 125 prepubertal children with CRI revealed significantly greater first-year (10.7 ± 3.1 cm/year) and second-year (7.8 ± 2.1 cm/year) growth rates in the rhGH-treated group.⁵ A beneficial effect on final height potential was reported in one study of 38 rhGH-treated children with CRI, who reached a final height 1.4 SDs (~ 9.8 cm) above standardized height at baseline. This was compared with a mean final height of 50 nontreated matched control children with CRI that was 0.6 SD (~ 4.2 cm) below standardized height at baseline.⁶ Data from the North American Pediatric Transplant Cooperative Study show that mean adult height SD scores, when compared with baseline height SD scores, increased by 0.70 (~ 4.9 cm), 0.35 (2.5 cm), and 0.49 (3.5 cm) in rhGH-treated patients with CRI, patients on dialysis, and transplant patients, respectively.⁷ Individual responsiveness to rhGH seems inversely related to the degree of impairment in renal function and metabolic compromise.

SGA

Three or more years of rhGH treatment in children born SGA sustains an accelerated growth rate and normalization of height and other anthropometric measurements (including head circumference), in contrast to untreated SGA control subjects.⁸⁻¹² Adult height outcomes are improved by treatment initiation at an early age and use of higher-dose rhGH (0.47 mg/kg per week in the peripubertal years). A recent controlled study, using a group of nontreated SGA children in an observational-group study design, reported that rhGH treatment in SGA children during puberty increased mean adult heights by 2.7 cm in boys and 4.2 cm in girls. Twenty-seven percent of control patients and 47% of treated patients had adult heights in the normal range for the general population (at least -2 SDs).¹³ The greatest gains in height were made by those children treated for longer than 2 years before the onset of puberty.

PWS

Children with PWS, who usually have deficient GH secretion, show growth-rate increases in response to rhGH therapy similar to other severely GHD children. In one study, sustained treatment for 3 to 4 years with increasing doses of rhGH increased mean height SD score by 1.8 ± 0.6 . (~ 12.6 cm).¹⁴ In a group of 11 Japanese children with PWS treated for >5 years, males were a mean of 10.3 cm taller and females 6.5 cm taller than same-gender untreated control patients with PWS.¹⁵ In addition, rhGH therapy increases lean body mass and energy

expenditure, decreases fat mass, and increases bone mineral density in children with PWS.¹⁶ These effects are matched by measurable functional benefits, including increases in strength and agility and ventilation drive in children,^{17,18} and acquisition of motor skills in infants with PWS.¹⁹ Changes in body composition and physical function are dose-dependent and attenuate but do not regress during prolonged rhGH therapy.¹⁴

ISS

Long-term rhGH therapy can lead to increased adult height in children with ISS, but the degree and predictability of this effect remains uncertain. Only 2 studies in the 1990s reported final heights greater than pretreatment predicted heights, and only 1 study reported an improved proportion of subjects with final height greater than the midparental target height.²⁰ A subsequent study of 80 non-GHD children treated with rhGH showed a mean (\pm SD) difference between predicted and adult height achieved among boys of $5.0 (\pm 5.1)$ cm and $5.9 (\pm 5.2)$ cm among girls; still, only a few subjects achieved their midparental target height.²¹ Importantly, in non-controlled studies such as these, height gain attributed to rhGH can be overestimated, because most untreated children with ISS show a spontaneous increase in height SD scores with age. A meta-analysis of controlled and noncontrolled studies suggested an average gain in adult height of ~ 1 cm per year of treatment.²² More recently, a randomized, placebo-controlled trial reported that a mean duration of 4.4 years of rhGH treatment (0.2 mg/kg per week administered three times weekly) increased adult height outcomes by a mean of 3.7 cm.²³ A separate study showed that use of a higher dosage of daily rhGH (0.37 vs 0.24 mg/kg per week) increased the mean difference between measured and predicted adult height from 5.4 to 7.2 cm.²⁴

On the basis of these data, in 2003 the Food and Drug Administration (FDA) approved rhGH therapy for ISS, defined as a height >2.25 SDs below the mean or less than the 1.2 percentile for age and gender with height predictions below 5 ft, 3 in (160 cm) (males) or 4 ft, 11 in (150 cm) (females) and without evidence of underlying disease or GHD. Use of rhGH for this indication remains controversial because of the variability in reported height improvement, poorly defined and documented measures of therapeutic success (eg, improved psychosocial adjustment), and debate about whether the goal of treatment should be simply a "normal" height or maximum height. Importantly, this indication for GH therapy is the only one that includes a threshold-height criterion for initiation.

DOES rhGH TREATMENT ALLAY DISABILITIES OF SHORT STATURE?

Once shown to be effective, FDA approval of rhGH therapy for indications other than GHD seemed logical, be-

cause some children with TS, CRI, SGA, and ISS are as short as those affected by GHD; however, selecting which of these children are sufficiently disadvantaged by height to warrant treatment remains problematic. In a minority of cases, when severe short stature is physically debilitating, treatment decisions are clear. Many (but not all) children with TS, CRI, and SGA and some (but not most) of the much larger number of children with ISS will have growth patterns of this severity. The average rhGH treatment gains described above will allow some of these children to achieve a height closer to or within the lower adult normal range. However, the majority of non-GHD children currently treated with rhGH is not truly physically disabled by diminished height.

Without clear evidence for physical disability, enthusiasm for rhGH therapy for short stature is traditionally rooted in the assumption that short stature is psychologically disabling and that taller stature as the result of rhGH therapy will lead to better psychosocial function. Both assumptions are currently being challenged. Although short stature can be associated with psychosocial stresses such as being teased and perceived as younger than actual age, in well-designed studies these experiences are not associated with psychological dysfunction.²⁵ Because psychological problems are not common in short children, it is not surprising that rigorously designed studies fail to demonstrate a relationship between adult height of rhGH-treated individuals and quality of life.²⁶⁻²⁸ Even in girls with TS, height at the conclusion of rhGH therapy does not contribute substantively to quality of life.²⁹

This lack of evidence for predictable psychological benefit in otherwise healthy children with ISS should not be interpreted to mean that no short children should be treated with rhGH. In children with TS or CRI, the stress of dealing with other comorbidities could amplify an adverse psychological effect of short stature. Even in otherwise healthy children, although difficult to define, some degree of disordered growth ought to be, like disfiguring physical traits, considered appropriately within the realm of medicine.

WHAT ARE THE RISKS?

Long-term data from large numbers of patients enrolled in postmarketing registries indicate that rhGH therapy is generally safe. In children with ISS, this observation is supported by 2 recent postmarketing trial reports.^{30,31} Insulin sensitivity is impaired by GH excess, and although some studies show an increase in insulin levels (eg, in patients with TS),³² overt diabetes mellitus is rare.^{30,31,33} Other events rarely reported in association with rhGH treatment include benign intracranial hypertension, slipped capital femoral epiphysis, scoliosis, features of acromegaly, and pancreatitis.³³ To date, these and other potential adverse effects of rhGH therapy (eg, reduced testicular volume, gynecomastia, deterioration

of renal function in patients with CRI, cardiac ventricular hypertrophy in patients with TS) have not been considered to be of sufficient clinical significance to alter prescribing.³⁴

One notable exception is the possible association of rhGH therapy and sudden respiratory death in children with PWS. These events have occurred predominantly in markedly obese patients in association with respiratory infections.³⁵ Although a causative role for rhGH remains unproven, these reports have led to precautionary labeling and recommendations for special pretreatment evaluation (eg, sleep studies) and monitoring during early therapy.^{16,35,36}

GH raises serum concentrations of insulin-like growth factor I, which is mitogenic and antiapoptotic, prompting concerns that rhGH therapy could facilitate development of cancers. Nearly 20 years of data from the largest GH-treatment registry, the National Cooperative Growth Study (NCGS),^{33,37} and from Japan³⁸ (where the first concerns about this association were raised) indicate that long-term use of rhGH is not associated with an increased risk of primary leukemia or other malignancies in patients without risk factors for cancer. In addition, a retrospective analysis of the NCGS found no evidence of an increased risk of developing an extracranial, nonleukemia neoplasm in rhGH-treated patients.³⁹

In summary, experience during the past 20 years has shown rhGH therapy to be generally safe in non-GHD children with short stature. However, continued surveillance of possible long-term effects of higher-dose rhGH therapy is paramount because (1) pharmacologic doses used to treat non-GHD short children continue to rise in response to dose-related improvements in growth outcomes, and the long-term risks of prolonged treatment of children with higher doses of rhGH remain unknown; (2) underreporting of adverse events is likely in postmarketing studies; and (3) potential adverse events could be separated from treatment by wide time periods. Thus, we should be careful that the paucity of reported adverse effects itself does not encourage expanded use of rhGH.⁴⁰ Although there seem to be few medical contraindications to rhGH therapy, the experience of transmission of Creutzfeldt-Jakob disease via pituitary GH is a poignant reminder to take a farsighted view of the potential ramifications of long-term hormonal therapy.

WHAT ARE THE COSTS?

Biosynthetic rhGH is expensive, and ethical considerations regarding its use are inextricably tied to this fact; for example, how should rhGH therapy be prioritized in the context of the American health care system that excludes >45 million people from any health insurance? Using traditional dosing guidelines, the annual cost for one child weighing 30 kg is approximately \$15 000 to 20 000. Treatment costs of adolescents using higher "pubertal" doses to maximize adult height can exceed

\$50 000 per year,⁴¹ and each inch of adult height gained is estimated to cost approximately \$35 000.^{22,42} Thus, treating even a 10% fraction of the children potentially eligible under the ISS indication (ie, ~0.1% of the childhood population) would cost hundreds of millions of dollars annually. Strategies to limit costs include targeting of dosage-by-weight treatment earlier in childhood and cessation of treatment at a “normal” rather than “maximum” height, both of which were designed to avoid years of high-dose, costly therapy during adolescence. Even so, those who prescribe and pay for rhGH treatment are increasingly confronted with the question of whether the morbidity of short stature and the benefits of the intervention justify its cost.^{40,43}

BALANCING BENEFITS AND THE BURDENS

Like any medical intervention, the merits of rhGH therapy for patients with short stature are judged by weighing the morbidity of the untreated condition and benefits arising from treatment against costs, risks, and potential alternatives. Current information reviewed above adds both clarity and complexity to this analysis. In general, height gain in short children treated with rhGH averages ~1.0 to 1.5 cm per year of treatment.²² Responses vary considerably, influenced by factors such as dosage,²⁴ degree of preexisting growth and skeletal age delay,²³ manipulation of puberty, and recently described polymorphisms in the GH receptor.^{44,45} With regard to psychosocial morbidity of short stature in childhood²⁵ and psychosocial benefits attributable to rhGH,²⁹ both seem to be less than previously presumed. Costs of therapy remain high, although the actual “dollars per milligram” price of rhGH has changed little over the past 2 decades. Thus far, risks remain low but must be constantly reassessed as dosages used to optimize outcomes rise.^{40,42} In summary, efficacy of rhGH in statistically increasing height has been demonstrated, but efficacy in improving psychosocial function to a degree that justifies the costs and potential risks has not been shown.

How can these observations help to guide rhGH prescription, policy, and research? First, although it is reasonable to consider children with heights below the first percentile (the threshold criteria for rhGH treatment of ISS) to be possible candidates for rhGH therapy, it is equally important to acknowledge that only a fraction of these children have a problem that can be helped by rhGH. Given uncertain and poorly defined psychosocial benefits, it seems increasingly prudent to advise non-treatment unless evidence for physical or psychological disability is clear. Informative and honest counseling of patients and families should include discussion of realistic and variable height-addition benefits, limited evidence for psychosocial benefit, and less expensive and less invasive alternative approaches (eg, counseling, oral oxandrolone).⁴⁶

Once a height within the normal adult range is

achieved, additional height-gain “benefit” of rhGH therapy becomes relative to the height of others (ie, social and economic advantages of a now-taller rhGH-treated person accruing at the expense of a shorter person who did not have access to rhGH), such that individual interest in greater height does not necessarily correlate with the societal interest. Therefore, treatment supported by public or insurance funds can be best justified by adhering to the principle of lessening disability and not maximizing height, with cessation of rhGH treatment when a normal adult height, rather than a maximum height, is achieved.⁴⁷ Because there is no compelling ethical reason to use rhGH to make some children taller than other normal-statured, nontreated children, treatment to enhance height within the normal range, if desired, should be paid for by private funds. Finally, future clinical research could help reduce the risks and costs by investigating the most efficient use of rhGH to achieve a satisfactory therapeutic outcome, redirecting the long-standing emphasis on strategies for maximizing height outcomes.

These observations and other realities are creating a fast-changing landscape for rhGH therapy. Increasingly, cost-saving efforts by hospital formularies, insurance providers, and government agencies are leading to price-reduction agreements with selected rhGH-producing companies. As a consequence, physician choice in prescribing is restricted, requiring use of particular (although essentially identical) rhGH products for indications for which they are not FDA-approved. In this environment, diminished costs of treatment will likely be matched by diminished motivation for manufacturers to continue marketing and researching rhGH. At the same time, alternative height-promoting therapies such as aromatase inhibition⁴⁸ or estrogen receptor–modulation⁴⁹ therapy to slow bone-age maturation during puberty offer novel competing approaches for the treatment of severe short stature. Given these trends, combined with uncertainties about the clinical significance of rhGH-mediated height gain and associated psychosocial well-being, it is plausible, if not likely, that enthusiasm and support for rhGH treatment of short stature will wane in the future. Responsible prescribing now will help to protect the availability of rhGH treatment for those relative few who truly need it.

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OFF LABEL, OFF BASE?

“Every day in medical offices around the country, physicians hand patients prescriptions for drugs to treat conditions for which the medicines haven’t been approved. Once a drug is approved by the Food and Drug Administration (FDA), a doctor can, with rare exceptions, legally prescribe it ‘off label’: for use as he or she sees fit. . . . Off-label use of drugs may be axiomatic in medicine, but a new study published in the Archives of Internal Medicine finds that the practice is frequently grounded more in anecdote than in hard science. Using data from a national survey of 3,500 office-based physicians, researchers found that 21 percent of the 725 million prescriptions written in 2001 were for off-label uses. Seventy-three percent of these prescriptions lacked strong scientific justification, such as a clinical trial, and were based on observational studies, case reports or no discernable evidence. And without solid evidence of safety and effectiveness, the researchers maintain, consumers run the risk of taking ineffective, expensive and potentially dangerous drugs. . . . In psychiatry, for example, researchers found that 96 percent of off-label prescriptions lacked strong scientific support.”

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Noted by JFL, MD

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