

High Dose Recombinant Human Growth Hormone (GH) Treatment of GH-Deficient Patients in Puberty Increases Near-Final Height: A Randomized, Multicenter Trial*

NELLY MAURAS, KENNETH M. ATTIE, EDWARD O. REITER, PAUL SAENGER, JOYCE BAPTISTA, AND THE GENENTECH, INC., COOPERATIVE STUDY GROUP†

Nemours Children's Clinic and Research Programs (N.M.), Jacksonville, Florida 32207; Baystate Medical Center (E.O.R.), Springfield, Massachusetts 01199; Montefiore Medical Center (P.S.), Bronx, New York 10467; and Genentech, Inc. (K.M.A., J.B.), South San Francisco, California 94080

ABSTRACT

GH production rates markedly increase during human puberty, mostly as an amplitude-modulated phenomenon. However, GH-deficient children have been dosed on a standard per kg BW basis similar to prepubertal children. This randomized study was designed to compare the efficacy and safety of standard recombinant human GH (rhGH) therapy (group I, 0.3 mg/kg-week) vs. high dose therapy (group II, 0.7 mg/kg-week) in GH-deficient adolescents previously treated with rhGH for at least 6 months. Ninety-seven children with documented evidence of GH deficiency (peak GH in response to stimuli, <10 ng/mL), with either organic or idiopathic pathology, were recruited. Both groups were matched for sex (group I, 42 males and 7 females; group II, 41 males and 7 females), age [group I, 14.0 ± 1.6 (\pm SD) yr; group II, 13.7 ± 1.6], standardized height (group I, -1.4 ± 1.1 ; group II, -1.2 ± 1.1), bone age (group I, 13.1 ± 1.3 yr; group II, 13.1 ± 1.3) etiology, maximum stimulated GH, previous growth rate, and midparental target height. All subjects were in puberty (Tanner stage 2–5) at study entry.

Of the 97 subjects enrolled, 45 were treated for 3 yr or more; 48 completed the study. Of the subjects who discontinued the study, the most common reason was satisfaction with their height, although others discontinued for adverse events or personal reasons. The frequency of patients who discontinued was the same in both groups. The primary efficacy analysis was the difference between dose groups for near-adult height, defined as the height attained at a bone age of 16 yr or more in males and 14 yr or more in girls; all subjects who

qualified were included in the analysis. This difference was statistically significant at 4.6 cm by analysis of covariance (ANCOVA; $P < 0.001$; $n = 75$). For subjects who received at least 4 yr of rhGH treatment, the difference between dose groups at that time point was 5.7 cm (by ANCOVA, $P = 0.024$; $n = 20$). The mean height SD score at near-adult height was -0.7 ± 0.9 in the standard dose group and 0.0 ± 1.2 in the high dose group. At 36 months the cumulative change in height (centimeters) was 21.5 ± 5.3 cm (group I) vs. 25.1 ± 4.9 cm (group II; $P < 0.001$, by ANCOVA); the change in Bayley-Pinneau predicted adult height was 4.8 ± 4.2 cm (group I) vs. 8.4 ± 5.7 cm (group II; $P = 0.032$). Median plasma IGF-I concentrations at baseline were $427 \mu\text{g/L}$ (range, 204–649) in group I and $435 \mu\text{g/L}$ (range, 104–837) in group II; at 36 months they were $651 \mu\text{g/L}$ (range, 139–1079) in group I vs. $910 \mu\text{g/L}$ (range, 251–1843) in group II ($P = \text{NS}$). No difference in change in bone age was detected between groups at any interval. High dose rhGH was well tolerated, with a similar safety profile as standard dose treatment and no difference in hemoglobin A_{1c} or glucose concentrations between groups.

In summary, compared to conventional treatment, high dose rhGH therapy in adolescents 1) increased near-adult height and height SD scores significantly, 2) did not increase the rate of skeletal maturation, and 3) appears to be well tolerated and safe. In conclusion, high dose rhGH therapy may have a beneficial effect in adolescent GH-deficient patients, particularly those who are most growth retarded at the start of puberty. (*J Clin Endocrinol Metab* 85: 3653–3660, 2000)

THERE IS SUBSTANTIAL variation in GH production rates during the life span in humans. High GH production rates are observed in newborns (1), followed by the classical ultradian rhythms of childhood (2), a marked in-

crease in production in puberty, with a clear decline in GH production rates with age (3). Adiposity (4) and gender (5) also contribute to the variations in GH levels observed within these age groups.

During human puberty there is an approximate doubling

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Address all correspondence and requests for reprints to: Nelly Mauras, M.D., Division of Endocrinology, Nemours Children's Clinic, 807 Nira Street, Jacksonville, Florida 32211. E-mail: nmauras@nemours.org.

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† The investigators who participated in this study as part of the Genentech, Inc., Cooperative Study Group are: Gilbert P. August, M.D., at Children's Hospital National Medical Center (Washington, DC); Jennifer J. Bell, M.D., at Columbia Presbyterian Medical Center (New York, NY); Thomas P. Foley, Jr., M.D., at Children's Hospital of Pittsburgh (Pittsburgh, PA); Ronald W. Gotlin, M.D., at The Children's Hospital (Denver, CO); Madeleine D. Harbison, M.D., at New York Hospital-Cornell Medical Center (New York, NY); Raymond L. Hintz, M.D., at Stanford University Medical Center (Palo Alto, CA); Nancy J. Hopwood, M.D., at University of Michigan Medical Center (Ann Arbor, MI);

Margaret H. MacGillivray, M.D., at Children's Hospital of Buffalo (Buffalo, NY); Nelly Mauras, M.D., at Nemours Children's Clinic (Jacksonville, FL); Wayne V. Moore, M.D., Ph.D., at Children's Mercy Hospital (Kansas City, MO); Thomas Moshang, M.D., at Children's Hospital of Philadelphia (Philadelphia, PA); Katrina L. Parker, M.D., at University of Alabama School of Medicine (Birmingham, AL); Leslie P. Plotnick, M.D., at Johns Hopkins Hospital (Baltimore, MD); Edward O. Reiter, M.D., at Baystate Medical Center (Springfield, MA); Alan D. Rogol, M.D., Ph.D., at University of Virginia Health Sciences Center (Charlottesville, VA); William E. Russell, M.D., at Vanderbilt University Medical Center (Nashville, TN); Paul Saenger, M.D., at Montefiore Hospital (Bronx, NY); Dennis M. Styne, M.D., at University of California (Davis, CA); Thomas A. Wilson, M.D., at State University of New York Health Sciences Center (Stony Brook, NY); and David T. Wyatt, M.D., at MACC Fund Research Center (Milwaukee, WI).

of GH production rates (6), with peak production coinciding with peak height velocity (2). This increase in GH secretory rates is clearly mediated at least in part through sex steroid hormones, and in both testosterone-treated and estradiol-treated prepubertal children there is an augmentation of the GH production rates, mostly as an amplitude-modulated phenomenon, relatively independent of changes in pulse frequency (7–9). Nonaromatizable androgens such as oxandrolone (10) and dihydrotestosterone (11) have been shown to have no impact on GH production, whereas estrogen receptor blockade with tamoxifen decreases GH production in pubertal males (12). Taken in aggregate, these and other data suggest that estrogens are the main feedback regulator of the increased GH production observed in puberty.

The pubertal growth spurt accounts for approximately 17% of adult male height and 12% of adult female height (13); these differences are largely responsible for differences in the final height of adult men and women (14). Compared to normal adolescents, studies in children with GH deficiency (GHD) have shown that pubertal development may be impaired, with abnormalities in both the timing and the duration of puberty observed (15–19). Even though there is wide availability in western countries of recombinant human GH (rhGH), and there have been measurable increases in growth rate and final height documented in GH-treated GH-deficient children (20), delays in diagnosis are common, with many children not reaching their full genetic height potential despite GH treatment (20, 21). Strategies to increase final height in GH-deficient patients receiving GH therapy have hence included suppression of the hypothalamic-pituitary-gonadal axis with GnRH analogs. The latter has been relatively successful in increasing final height or predicted adult height in some studies, but not others (22–27). The consequences of this approach however, as it pertains to bone accretion/bone density and the psychological impact of suppressing the timely course of puberty in an already short child have not been appropriately studied to date.

As physiological data in puberty indicate that GH production is much higher during human puberty than at any other time, and the doses of GH have been traditionally kept constant on a milligram per kg basis, we designed this study to determine whether more than doubling the GH dose in GH-deficient patients in puberty would significantly increase their growth rates without undue advancement of bone age, thus improving adult height. A multicenter, randomized, two-dose study was performed until near-adult height was reached.

Subjects and Methods

Study subjects

Twenty centers in the U.S. participated in this multicenter trial. The study protocol was approved by each local institutional review board. Ninety-seven subjects (83 males and 14 females) with GHD participated in this trial after obtaining informed written consent and child's assent. GHD was defined as peak GH levels of less than 10 ng/mL before original GH treatment by two standard stimulation tests. Inclusion criteria demanded that all subjects had been treated with GH for at least 6 months before the studies, and they had to be in puberty, but with residual height potential. The males were aged 10–18 yr, with testis volume of 4 mL or more and bone age of 14 yr or greater; the females were aged 8–16 yr, with Tanner breast stage of 2 or more and bone age of 12 yr or greater. The T_4 level had to be within normal limits. ACTH- and gonadotropin-deficient subjects were excluded from participation as well as those who had been previously treated with sex steroids, had a history of malignancy treated within the past year, had undergone spinal irradiation, or had other causes of growth failure (systemic illnesses, skeletal dysplasias, and chromosomal anomalies, including Turner's syndrome). The baseline clinical characteristics of the patients are summarized in Table 1. There were no significant differences between the two treatment groups for any of the baseline parameters.

Experimental design

All patients were randomly assigned to continued treatment with GH (Nutropin, Genentech, Inc., South San Francisco, CA) at either 0.3 mg/kg-week (standard dose) or 0.7 mg/kg-week (high dose), sc, daily. Subjects were randomized to either the standard dose or the high dose arm in such a way as to maintain a balance with respect to sex, schedule of

TABLE 1. Demographic and baseline characteristics

	Standard dose 0.3 mg/kg-wk (n = 49)	High dose 0.7 mg/kg-wk (n = 48)
Sex (no.)		
Male	42	41
Female	7	7
Etiology of GHD (no.)		
Idiopathic	47	45
Organic	2	3
Race (no.)		
Caucasian	45	45
Black	2	0
Hispanic	2	3
Asian	0	0
	Mean ± SD (range)	
Age (yr)	14.0 ± 1.6 (10.7–17.1)	13.7 ± 1.6 (10.6–16.3)
Bone age (yr)	13.1 ± 1.3 (10.0–15.5)	13.1 ± 1.3 (n = 47) (9.6–15.2)
Tanner stage	3.0 ± 1.0 (2–5)	2.9 ± 0.8 (2–5)
Previous growth rate (cm/yr)	8.5 ± 1.8 (n = 47) (5.3–12.7)	8.5 ± 2.2 (n = 47) (4.0–15.0)
Duration of previous GH treatment (yr)	3.5 ± 2.6 (0.5–9.7)	4.1 ± 2.9 (0.6–10.8)
Height (cm)	151.9 ± 9.3 (134.8–170.7)	151.7 ± 9.4 (131.2–168.2)
Height SD score	–1.4 ± 1.1 (–3.4 to 1.7)	–1.2 ± 1.1 (–4.5 to 1.3)
Maximum stimulated GH (μg/L)	5.7 ± 2.6 (1.2–9.9)	5.3 ± 2.7 (1.1–9.8)
Bayley-Pinneau predicted adult height SD score	–1.1 ± 1.1 (–3.1 to 1.0)	–0.9 ± 1.2 (n = 47) (–3.2 to 2.5)
Mid-parental target height SD score	–0.4 ± 0.8 (n = 48) (–2.1 to 1.4)	–0.3 ± 0.7 (n = 46) (–1.4 to 1.1)

previous GH therapy (three times weekly or daily), bone age, chronological age, pubertal status (Tanner stage), previous 1-yr growth rate, height standardized by age and sex, and study center. Patients were seen as out-patients at 3-month intervals for up to 63 months, and physical exam and blood and urine tests were performed. Bone ages were determined every 6 months for the duration of the study.

Treatment with GH was discontinued at near-adult height, defined as a bone age of 16 yr or more for males and 14 yr or more for females and a growth rate less than 2 cm/yr for 1 yr. Adult height was defined as epiphyseal closure on hand-wrist bone age x-ray and no change (<1 cm) in height for 12 months. Dual emission x-ray absorptiometry (DEXA) scans (whole body and antero-posterior spine) for assessment of bone mineral density (BMD) were taken at or within 1 month of treatment discontinuation using either Hologic, Inc., 1000, 2000, or 4000 instruments (Hologic, Inc., Waltham, MA) or Lunar Corp. equipment (Lunar Corp., Madison, WI).

Sex steroid replacement therapy was allowed during the study in only four subjects; this was an institutional review board-approved amendment of the study. As the patients were in puberty at study entry, these subjects were considered to have developed hypogonadism and arrested puberty.

Assays and x-rays

Blood was withdrawn for measurement of complete blood count, chemistry panel, and T₄ and urinalysis was performed every 3 months for the first 36 months of the trial and yearly subsequently for the next 3 yr in those subjects still enrolled at that time. A 2-h glucose tolerance test was performed at baseline, 3 months, 12 months, and yearly thereafter for up to 72 months for the measurement of glucose, insulin, C peptide, and hemoglobin A_{1c} (HbA_{1c}) levels. All of these assays were run by standard automated analyzers at SmithKline Beecham (Dublin, CA). Serum testosterone concentrations (males) and estradiol concentrations (females) were measured every 6 months during the study by immunoassays at SmithKline Beecham. Plasma insulin-like growth factor I (IGF-I) concentrations and GH antibody titers were measured at 3-month intervals for the first 24 months and then at 6-month intervals for up to 72 months. IGF-I was assayed at Genentech, Inc., after acid-ethanol extraction as previously described (28). GH antibodies were measured by RIA at Genentech, Inc. Bone age determinations of the left hand and wrist were performed by Fels Institute (Yellow Springs, OH); the readers were blinded to the treatment arm. Predicted adult heights were estimated based on the Bayley-Pinneau table (29). DEXA scans were performed locally at each site and were read at a central location by Hologic, Inc.

Statistical analysis

Fisher's exact test for proportions, the two-sample *t* test for between-group comparisons, and the paired *t* test for within-group changes were used for assessments of safety and efficacy. The significance level for all comparisons was 0.05; no adjustments were made for multiple testing. Log values were used when necessary because of skewed data.

The target primary measure of efficacy was adult height, however, there were a limited number of subjects who had reached adult height. Therefore, near-adult height was used as the primary efficacy variable. If bone age was missing at the last measured height, it was extrapolated from the previous bone age using the change in chronological age; this extrapolation was not used in any other analysis. The standard and high dose groups were compared for near-adult height using analysis of covariance (ANCOVA) with the protocol-defined covariates of sex, previous growth rate, schedule for previous GH therapy, baseline height, chronological age, bone age, and pubertal status (Tanner stage). An intent to treat analysis, including all enrolled subjects, was performed to support the primary analysis. In this analysis, the last measured height, obtained during treatment or at a posttreatment visit, was used for all subjects, including those in whom near-adult height was not achieved. BMD assessment was performed at study discontinuation only. To correct the spine BMD provided by DEXA for bone size, the bone mineral apparent density (BMAD) was calculated for the lumbar spine using the following equation: spine BMAD = bone mineral content (BMC) ÷ area^{3/2}. Total body bone mineral content (BMC) was partially corrected for body size, calculated as BMC ÷ height (30, 31). Because of

the limited amount of data collected, the analysis of these data is descriptive.

Results

Of the 97 subjects enrolled, 48 fully completed the study, and 49 subjects discontinued the study before completion. Six subjects discontinued because of adverse events (see below). Twenty-nine subjects, 12 in the standard dose group and 17 in the high dose group, requested early removal from the study for different reasons, including 1 subject in the standard dose group and 2 in the high dose group who were tired of taking injections and 5 subjects in the standard dose group and 6 in the high dose group who had personal, behavioral, or unknown reasons for stopping. The majority of subjects, 6 in the standard dose group and 9 in the high dose group, were satisfied with the height they had attained; the others were discontinued for noncompliance or protocol violations.

Near-adult height

Seventy-five subjects met the criterion for attaining near-adult height; of these, 41 required bone age to be extrapolated to the date of their last measured height to meet the criterion. Forty-two of the subjects who met the criteria for attaining near-adult height were in the standard dose and 33 were in the high dose group.

The standard and high dose groups were compared using ANCOVA using the covariates listed above. The use of sex steroid replacement therapy was a protocol-specified covariate; however, only four subjects received sex steroid therapy during the study, an inadequate number for use as a covariate. Based on ANCOVA, subjects in the high dose group were significantly taller at near-adult height than subjects in the standard dose group by an average of 4.6 cm (*n* = 75; *P* < 0.001; 95% confidence interval, 2.6–6.5 cm). The significant covariates were sex, baseline height, and bone age. The mean ± SD age at near-adult height was 17.2 ± 1.3 yr (range, 14.1–19.4 yr), with a mean bone age of 16.9 ± 0.9 yr (range, 14.2–18.2 yr). The mean duration of therapy was 3.0 ± 1.0 yr (range, 1.3–5.4 yr). There were no between-dose group differences at near-adult height in age, bone age, or duration of GH therapy. For subjects with near-adult height, the height SD score at last measured height was -0.7 ± 0.9 in the standard dose group and 0.0 ± 1.2 in the high dose group (*P* = 0.002). The change in height SD score was 0.6 ± 0.8 and 1.1 ± 1.0, respectively (*P* = 0.012).

Last measured height (intent to treat analysis)

In the intent to treat analysis, the last measured height was used for all subjects regardless of whether near-adult height was achieved. Using ANCOVA, subjects in the high dose group were taller at last measured height than those in the standard dose group by an average of 2.8 cm (*n* = 97; *P* = 0.036; 95% confidence interval, 0.2–5.3 cm). The significant covariates were sex, baseline height, age, and bone age. The mean ± SD age at last measured height was 17.0 ± 1.5 yr (range, 11.9–19.4 yr), with a mean bone age of 16.4 ± 1.3 yr (range, 12.3–18.2 yr). The mean duration of therapy was 2.7 ± 1.2 yr (range, 0–5.4 yr). There were no between-dose group

differences in age or bone age at last measured height or duration of GH therapy.

Change in height by duration of treatment

An additional analysis was performed for change in height by duration of treatment (by ANCOVA, using sex and baseline bone age as covariates). Subjects in the high dose group were taller than those in the standard dose group after 1 yr of therapy by an average of 1.6 cm ($n = 90$; $P < 0.001$). This difference increased with each subsequent year of treatment; after 2 yr the increase in stature was 2.4 cm ($n = 72$; $P = 0.002$); after 3 yr, it was 4.3 cm ($n = 45$; $P < 0.001$); and after 4 yr of therapy, subjects in the high dose group were taller than those in the standard dose group by an average of 5.7 cm ($n = 20$; $P = 0.024$).

Growth rate

The mean prestudy growth rate was 8.5 cm/yr in both groups for subjects completing month 12 of the study. The mean month 0–12 growth rate was 9.8 cm/yr in the high dose group ($n = 44$) compared with 8.2 cm/yr in the standard dose group ($n = 43$; $P = 0.001$ between groups). Improved mean growth rates were sustained in the high dose group relative to the standard dose group in subjects completing months 12–24 of the study, although this difference did not attain statistical significance ($n = 69$; $P = 0.063$). The difference between treatment groups in growth rate was more pronounced at months 24–36, reaching statistical significance despite the reduced number of subjects ($n = 41$; difference, 1.7 cm/yr; $P = 0.038$). Data for subjects completing 3 yr of treatment ($n = 41$) are shown in Fig. 1.

Standardized height

The mean height SD score was more than 1 SD below the mean in both treatment groups at baseline. The mean change in height SD score was significantly greater in the high dose group for months 0–12 (0.6 ± 0.3 vs. 0.4 ± 0.4 ; $n = 45$ in each group; $P = 0.024$ between groups). The difference between groups for the mean change from baseline increased with continued therapy. As Fig. 2 illustrates, for subjects com-

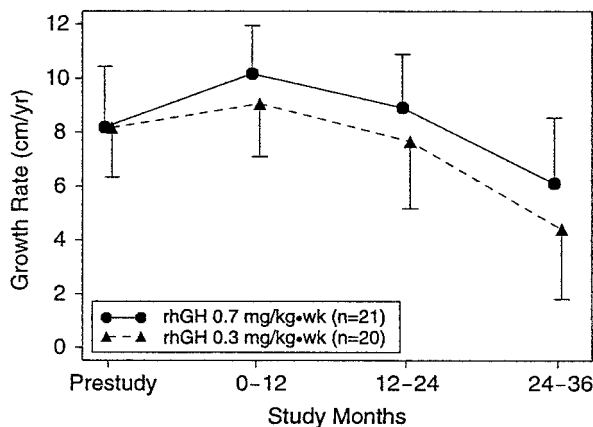


FIG. 1. Mean (\pm SD) growth rates (centimeters per yr) in pubertal GHD subjects treated for 36 months with standard doses of GH (0.3 mg/kg-week) or high doses (0.7 mg/kg-week).

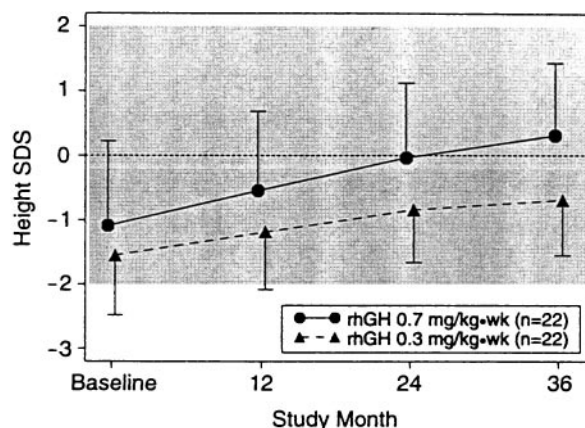


FIG. 2. Mean (\pm SD) height SD score (SDS) in pubertal GHD patients treated with standard vs. high dose GH.

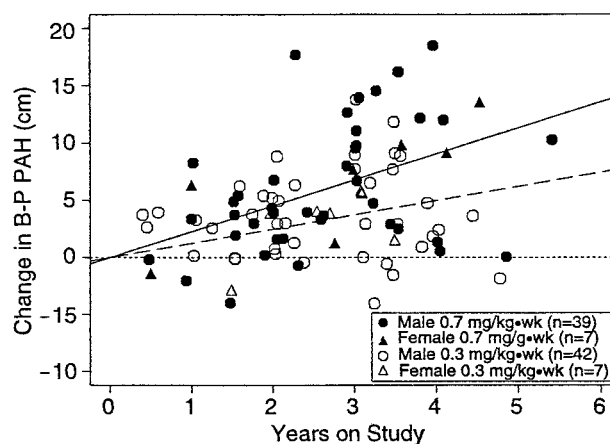


FIG. 3. Change in the predicted adult height by Bayley-Pinneau compared to baseline in GHD patients in puberty treated with two different doses. The solid line represents linear regression for subjects treated with 0.7 mg/kg-wk; the dashed line represents linear regression for subjects treated with 0.3 mg/kg-wk. The dotted horizontal line at 0 indicates no change from baseline and is provided as a visual reference.

pleting 3 yr of treatment, the mean change from baseline was 1.4 ± 0.8 in the high dose group ($n = 22$) compared with 0.9 ± 0.7 in the standard dose group ($n = 22$; $P = 0.023$ between groups).

Predicted adult height (PAH)

The Bayley-Pinneau (B-P) PAH is based on height and bone age measurements and is increasingly accurate as adult height is reached. The standardized B-P PAH was similar in the two treatment groups at baseline, at approximately 1 SD below the mean. After 3 yr, standardized B-P PAH improved by 1.3 SD, or 8.4 cm, in the high dose group ($n = 20$) compared with 0.8 SD, or 4.8 cm, in the standard dose group ($n = 20$; $P < 0.032$ between groups). The change from baseline to last PAH (or last measured height) increased over time at a greater rate in the high dose group, as shown in Fig. 3.

Weight and BMI

In the standard dose group ($n = 22$), body weight was 41.5 ± 9.2 kg at baseline and 61.9 ± 10.3 at 36 months,

whereas in the high dose group ($n = 22$) it was 41.0 ± 8.4 and 67.2 ± 15.0 at baseline and 36 months, respectively (by ANCOVA with covariate change in height, $P = 0.21$). Body mass index did not change significantly in either group (standard dose, 19.3 ± 3.6 kg/m² at baseline vs. 22.0 ± 3.6 at 36 months; high dose, 18.7 ± 2.3 vs. 22.3 ± 3.2 at baseline and 36 months, respectively).

Bone age and Tanner pubertal stage

The change in bone age during each year of therapy is a measure of the rate of skeletal maturation and is related to the tempo of pubertal progression. As shown in Fig. 4, the cumulative change in bone age was not statistically significantly different between the two treatment groups at 1, 2, or 3 yr, with a mean rate of advancement of approximately 1 yr/yr of treatment in both groups. Similarly, the rate of advancement in puberty, as assessed by Tanner pubertal stage for genitalia (males) or breasts (females), was similar in the two dose groups (data not shown).

IGF-I concentrations

Plasma IGF-I concentrations increased to a greater extent in the high dose group than in the standard dose group. Median values rose from 508 to 681 μ g/L in the high dose group at month 12 compared with a change from 427 to 589 μ g/L in the standard dose group and from 435 to 910 μ g/L in the high dose group at month 36 compared with a change from 427 to 651 μ g/L in the standard dose group. However, the differences between groups for the change from baseline, using log values or standardized scores, were not statistically significant at 1, 2, or 3 yr. Table 2 shows the median data in those subjects who had results available for 36 months. Mean IGF-I SD scores were within the high normal range in both groups during the study (see Fig. 5).

The frequency of IGF-I concentrations above the normal range during therapy was also compared between dose groups. Eight subjects, 1 in the standard dose group and 7 in the high dose group, had IGF-I levels above the normal range

at baseline. In addition, all 8 of these subjects had at least 1 high value during therapy. Excluding these subjects, 19 of 48 subjects (40%) in the standard dose group and 23 of 40 subjects (58%) in the high dose group had 1 or more elevated IGF-I levels during therapy after normal baseline values ($P = 0.133$ between groups). At any given point in time, approximately 28% of the patients in the high dose group and approximately 9% in the standard dose group had high IGF-I concentrations.

Secondary efficacy measure: BMD (Table 3)

Thirty-four subjects dropped out of the study before the protocol amendment allowing for BMD measures to be obtained at discontinuation, and 63 discontinued after that date. Of these 63 subjects, 31 had BMD DEXA scans. The groups did not differ in mean total body or spine BMD (grams per cm²), nor did they differ when the comparison was made based on z-scores (for age and sex). There was also no difference between groups for spine BMAD or total body corrected BMC. None of the measures of BMD showed a relationship to treatment duration or the subject's age. However, the average z-scores for the standard and high dose groups for total body (-0.9 and -0.8 , respectively) and spine (-1.0 and -0.2) were lower than those in the general population.

Adverse events

Overall, adverse events were reported in approximately equal percentages of subjects in the two treatment groups. There were no statistically significant differences in adverse events between treatment groups. Ten serious adverse events were reported during the study: four in the standard dose group and six in the high dose group (one subject in the high dose group reported two events). Of the serious adverse events, most were considered unrelated to GH therapy. One case of worsening scoliosis, which required surgery, was reported in each of the dose groups. These events were considered related to the rapid growth induced by GH and to the subject's underlying condition. One case of hip pain in the high dose group was considered to possibly be related to the study drug. Six subjects discontinued the study because of adverse events: two subjects in the standard dose group because of scoliosis and thigh pain, respectively, and four subjects in the high dose group because of broadening of the nasal bridge, large shoe size, ankle swelling, and right hip pain. Cases of hyperglycemia, peripheral edema, and myalgia were only reported for subjects in the standard dose group. Two cases of mild hypoglycemia were reported in the high dose group. No cases of leukemia, slipped capital femoral epiphysis, or intracranial hypertension were reported during the study.

Other laboratories

Laboratory studies generally showed no significant differences between groups. These assessments included frequent oral glucose tolerance tests and HbA_{1c} measurements. No statistically significant differences were noted between the two dose groups in glucose, insulin, and C peptide vari-

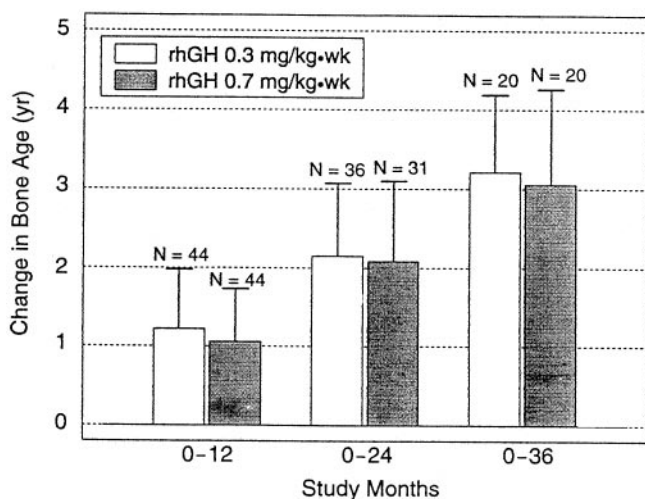


FIG. 4. Cumulative change in bone age compared to baseline in the same subjects treated with two doses of GH for up to 36 months. The number of subjects per time point is indicated.

TABLE 2. Median (range) plasma IGF-I concentrations ($\mu\text{g/L}$)

	Baseline	12 months	24 months	36 months	Change 0–36 months
0.3 mg/kg·w (n = 13)	427 (204–649)	559 (248–851)	651 (121–949)	651 (139–1079)	208 (–228 to 598)
0.7 mg/kg·w (n = 18)	435 (104–837)	671 (361–1046)	711 (421–1285)	910 (251–1843)	360 (–277 to 1604)

Normal concentrations in 12–16 yr: males, 202–957; females: 261–1096.

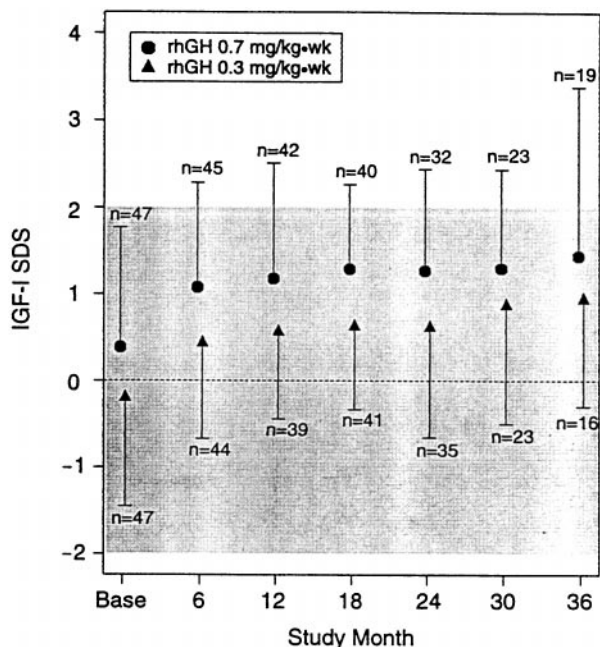


FIG. 5. IGF-I SD score (calculated for age- and sex-specific values) in the two groups of GH-deficient patients treated with two doses of GH.

ables, except for a greater increase in fasting insulin ($P = 0.011$) and C peptide ($P = 0.019$) in the high dose *vs.* standard dose group at 24 months. Median fasting and postprandial insulin and C peptide levels increased in both dose groups at various time points. Mean fasting and postprandial glucose levels were stable throughout the study, although sporadic high individual values were observed. Mean HbA_{1c} increased slightly within each dose group at 12 and 24 mo, returning to baseline values by 36 mo (Table 4).

Although three cases of eosinophilia in the high dose group were reported as adverse events, the mean counts did not change significantly in either dose group. The incidence of and titers to anti-GH antibodies were greatest at baseline and declined similarly in both dose groups during the study. All antibody binding capacity measurements were below 2 mg/L. There were no statistically significant differences between dose groups in mean change from baseline in testosterone or estrogen levels. Mean cholesterol levels decreased in both groups.

Discussion

The results of this study show a significant increase in growth and near-adult height in GHD adolescent youngsters treated with GH in high doses for at least 3 yr compared to the effects of conventional doses. Near-adult height data showed a net increase of 4.6 cm of height gain in the high dose group over the standard dose group. In subjects treated for 4 yr, the net gain was 5.7 cm ($P = 0.024$; $n = 20$), suggesting

that the potential net gain in height increases with years of treatment. Mean height SD score at near-adult height was -0.7 ± 0.9 in the standard dose group [as in previous studies (20)] and 0.0 ± 1.2 in the high dose group.

An interesting and important finding of these studies is the normal pace of bone maturation, with bone ages advancing approximately 1 yr/chronological yr in both the standard and high dose groups. This was also accompanied by comparable pubertal development in both groups as observed on physical exam. Taken in aggregate, these data indicate that GH therapy, even in high doses, does not abnormally advance skeletal maturation or affect the tempo of puberty in GHD children.

This conclusion contrasts with that reported by Stanhope *et al.* (32, 33), who studied 52 children with idiopathic isolated GHD treated with GH before puberty; once children reached puberty they were randomized to either GH at a standard dose of 15 IU/m²·wk (~ 0.2 mg/kg·wk) or a high dose of 30 IU/m²·wk (~ 0.4 mg/kg·wk). Four-year results showed no statistically significant difference in growth rates between the two groups, but there appeared to be an acceleration of pubertal maturation in boys on the higher dose regimen. As in our study, no difference was observed in the rate of bone age maturation. Even though we did not observe any deleterious effect of GH on the tempo of puberty, it is possible that the higher doses used in the present experimental paradigm (0.7 mg/kg·week) *vs.* the high dose reported in the Stanhope study (0.4 mg/kg·week) may explain the better outcome in terms of near-final height and growth performance reported here.

During no other time in postnatal development are there higher IGF-I concentrations than those observed during puberty, with the upper end of normal range in 12- to 16-yr-old males close to 1000 ng/mL in most assays. However, one concern with the use of increased GH doses is the potential effect of increasing plasma IGF-I concentrations to supra-physiological concentrations (34–36). In the present studies there was substantial variation in plasma IGF-I concentrations in both groups, with the change in concentration from baseline ranging from -228 to 598 $\mu\text{g/L}$ (median, 208) in the standard dose group *vs.* -277 to 1604 (median, 360) in the high dose group and no statistical difference between the groups. IGF-I levels above the normal range were observed in seven of the eight subjects in the high dose group at baseline. Even though the difference between groups was not statistically significant during treatment, the observation of overall higher levels in the high dose group requires careful follow-up of IGF-I concentrations in patients in whom these dose regimens are considered. Even though not customarily used by many in pediatric endocrine practice, the routine measurement of plasma IGF-I concentration during treatment with GH should help identify supra-physiological re-

TABLE 3. Changes in total body and lumbar bone mineral density (BMD) and BMD Z score by DEXA

Whole body	0.3 mg/kg·d	0.7 mg/kg·d
BMD (gm/cm ²)	1.054 ± 0.182 (0.668–1.340) n = 10	1.061 ± 0.113 (0.888–1.204) n = 10
BMD Z score	–0.92 ± 1.92 (–4.99 to 2.11) n = 10	–0.83 ± 1.20 (–2.66 to 0.66) n = 10
Corrected ^a BMC (gm/cm)	11.66 ± 4.18 (4.36–18.39) n = 12	13.23 ± 2.91 (9.00–16.62) n = 9
Lumbar		
BMD (gm/cm ²)	1.027 ± 0.178 (0.708–1.385) n = 15	1.150 ± 0.235 (0.840–1.529) n = 14
BMD Z score	–0.97 ± 1.02 (–2.56 to 0.58) n = 10	–0.21 ± 1.69 (–2.28 to 2.76) n = 11
Corrected ^a BMC (gm/cm)	0.136 ± 0.024 (0.100–0.184) n = 12	0.136 ± 0.025 (0.104–0.181) n = 12

^a Corrected BMC = BMC (gm)/height (cm).

TABLE 4. Carbohydrate metabolism

	Mean ± SD			
	Baseline	Month 12	Month 24	Month 36
HbA _{1c} (% total hemoglobin)				
0.3 mg/kg·wk (n = 39) ^a	5.2 ± 0.4	5.4 ± 0.4		
(n = 18) ^b	5.3 ± 0.4	5.4 ± 0.4	5.4 ± 0.4	5.1 ± 0.6
0.7 mg/kg·wk (n = 42) ^a	5.1 ± 0.4	5.3 ± 0.4		
(n = 18) ^b	5.1 ± 0.5	5.4 ± 0.5	5.3 ± 0.4	5.1 ± 0.6
Fasting glucose (mmol/L)				
0.3 mg/kg·wk (n = 43) ^a	4.9 ± 0.4	5.0 ± 0.6		
(n = 21) ^b	5.0 ± 0.3	5.0 ± 0.5	5.1 ± 0.3	5.2 ± 0.4
0.7 mg/kg·wk (n = 44) ^a	4.8 ± 0.5	5.0 ± 0.6		
(n = 21) ^b	4.9 ± 0.5	4.9 ± 0.4	5.3 ± 0.9	4.8 ± 0.8
Postprandial glucose (mmol/L)				
0.3 mg/kg·wk (n = 42) ^a	6.1 ± 1.6	6.0 ± 1.3		
(n = 17) ^b	5.4 ± 1.0	5.7 ± 1.0	5.5 ± 1.3	5.4 ± 1.2
0.7 mg/kg·wk (n = 40) ^a	5.7 ± 0.8	5.7 ± 1.5		
(n = 18) ^b	6.0 ± 0.9	6.2 ± 1.4	6.0 ± 1.1	5.8 ± 1.8
	Median (range)			
Fasting insulin (pmol/L)				
0.3 mg/kg·wk (n = 43) ^a	66 (24–186)	90 (24–666)		
(n = 21) ^b	72 (24–186)	90 (24–666)	72 (24–210)	120 (20–192)
0.7 mg/kg·wk (n = 42) ^a	66 (30–240)	96 (18–384)		
(n = 18) ^b	72 (30–120)	96 (4–162)	102 (42–240)	90 (30–348)
Postprandial insulin (pmol/L)				
0.3 mg/kg·wk (n = 44) ^a	240 (48–846)	270 (78–948)		
(n = 21) ^b	234 (72–474)	264 (78–930)	252 (60–690)	318 (66–942)
0.7 mg/kg·wk (n = 41) ^a	204 (54–1104)	330 (18–1194)		
(n = 17) ^b	204 (54–780)	366 (84–1194)	366 (120–1032)	216 (30–1320)

^a Data for subjects completing 12 months of treatment.

^b Data for subjects completing 36 months of treatment.

To convert glucose to mg/dL, multiply *18, insulin to μ U/mL divide by 6.

sponses to GH, allowing for the GH dose to be adjusted more appropriately for each individual patient.

The effect of high dose *vs.* standard dose GH on total body and spine BMD was also assessed in patients at the end of therapy (n = 31). There was no difference in total body BMD or bone mineral content (corrected for height) or spine BMD, BMD z-score, or BMAD (corrected for bone size) between the two groups. However, the average z-scores for total body and spine BMD were lower than those of age- and sex-matched controls, congruent with the previous finding that young patients with GHD are at risk for reduced bone mass (37, 38).

The incidence of various adverse events was approximately equal in the two dose groups, with no significantly

greater frequency of adverse effects clearly associated with the increased GH dose. Laboratory studies generally showed no significant differences between groups, and measurable titers to anti-GH antibodies were greatest at baseline and declined similarly in both dose groups during the study. There was no evidence of worse carbohydrate tolerance in the high dose group. Of the serious adverse events, most were considered unrelated to GH therapy. One case of worsening scoliosis, which required surgery, was reported in each of the dose groups.

In summary, a mean of 3 yr of high dose GH therapy to GHD adolescent children was associated with a statistically significant increase in near-adult height of 4.6 cm over that in children treated with standard doses of GH; in those

treated for 4 yr, the increase was 5.7 cm. This was not associated with an undue advancement of skeletal maturation, alteration of the tempo of puberty, or greater frequency of adverse events. We conclude that high dose GH therapy, administered during a finite window of time, may be beneficial and safe in increasing the final adult height of youngsters with GHD who are in the midst of puberty. This may be particularly useful in those most growth retarded at the start of puberty. This strategy warrants careful monitoring of IGF-I concentrations and continued surveillance for adverse events.

References

1. Wright NM, Northington FJ, Miller JD, Veldhuis JD, Rogol AD. 1992 Elevated growth hormone secretory rate in premature infants: deconvolution analysis of pulsatile growth hormone secretion in the neonate. *Pediatr Res.* 32:286–290.
2. Martha PM, Rogol AD, Veldhuis JD, Kerrigan JR, Goodman DW, Blizzard RM. 1989 Alterations in the pulsatile properties of circulating growth hormone concentrations during puberty in boys. *J Clin Endocrinol Metab.* 69:563–570.
3. Giustina A, Veldhuis JD. 1998 Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. *Endocr Rev.* 19:717–797.
4. Weltman A, Weltman JY, Hartman ML, et al. 1994 Relationship between age, percentage body fat, fitness and 24h GH release in healthy young adults: effects of gender. *J Clin Endocrinol Metab.* 78:543–548.
5. Jaffe CA, Ocampo-Lim B, Guo W, et al. 1998 Regulatory mechanisms of growth hormone secretion are sexually dimorphic. *J Clin Invest.* 102:153–164.
6. Rose SR, Municchi G, Barnes KM, et al. 1991 Spontaneous growth hormone secretion increases during puberty in normal girls and boys. *J Clin Endocrinol Metab.* 73:428–435.
7. Mauras N, Blizzard RM, Link K, Johnson ML, Rogol AD, Veldhuis JD. 1987 Augmentation of growth hormone secretion during puberty: evidence for a pulse amplitude-modulated phenomenon. *J Clin Endocrinol Metab.* 64:596–601.
8. Mauras N, Rogol AD, Veldhuis JD. 1989 Specific time-dependent actions of low-dose ethinyl estradiol administration on the episodic release of GH, FSH and LH in prepubertal girls with Turner's syndrome. *J Clin Endocrinol Metab.* 69:1053–1058.
9. Mauras N, Rogol AD, Veldhuis JD. 1990 Increased hGH production rate after low-dose estrogen therapy in prepubertal girls with Turner's syndrome. *Pediatr Res.* 28:626–630.
10. Link K, Blizzard RM, Evans WS, Kaiser DL, Parker MW, Rogol AD. 1986 The effect of androgens on the pulsatile release and the twenty-four-hour mean concentration of growth hormone in peripubertal males. *J Clin Endocrinol Metab.* 62:159–164.
11. Veldhuis JD, Metzger DL, Martha PM, et al. 1997 Estrogen and testosterone, but not a nonaromatizable androgen, direct network integration of the hypothalamo-somatotrope (GH)-IGF-I axis in the human: evidence from pubertal pathophysiology and sex steroid hormone replacement. *J Clin Endocrinol Metab.* 82:3414–3420.
12. Metzger DL, Kerrigan JR. 1994 Estrogen receptor blockade with tamoxifen diminishes GH secretion in boys: evidence of a stimulatory role of endogenous estrogens during male adolescence. *J Clin Endocrinol Metab.* 79:513–518.
13. Tanner JM, Davies PSW. 1985 Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr.* 107:317–329.
14. Bourguignon JP. 1988 Linear growth as a function of age at onset of puberty and sex steroid dosage: therapeutic implications. *Endocr Rev.* 9:467–488.
15. Goodman HG, Grumbach MM, Kaplan SL. 1968 Growth and growth hormone. II. A comparison of isolated growth-hormone deficiency and multiple pituitary-hormone deficiencies in 35 patients with idiopathic hypopituitary dwarfism. *N Engl J Med.* 278:57–68.
16. Rimoin DL, Merimee TJ, McKusick VA. 1966 Growth-hormone deficiency in man: an isolated recessively inherited defect. *Science.* 152:1635–1637.
17. Tanner JM, Whitehouse RH, Hughes PCR, Carter BS. 1976 Relative importance of growth hormone and sex steroids for the growth at puberty of trunk length, limb length, and muscle width in growth hormone-deficient children. *J Pediatr.* 89:1000–1008.
18. Codner E, Mericq V, Cassorla F. 1997 Optimizing growth hormone therapy during puberty [Review]. *Horm Res.* 48(Suppl 5):16–20.
19. Darendeliler F, Hindmarsh PC, Preece MA, Cox L, Brook CGD. 1990 Growth hormone increases rate of pubertal maturation. *Acta Endocrinol (Copenh).* 122:414–416.
20. Blethen SL, Baptista J, Kuntze J, Foley T, Lafranchi S, Johanson A. 1997 Adult height in growth hormone (GH)-deficient children treated with biosynthetic GH. The Genentech Growth Study Group. *J Clin Endocrinol Metab.* 82:418–420.
21. Root W, Kemp SF, Rundle AC, Dana K, Attie KM. 1998 Effect of long-term recombinant growth hormone therapy in children: The National Cooperative Growth Study, USA, 1985–1994. *J Pediatr Endocrinol Metab.* 11:403–412.
22. Pasquino AM, Municchi G, Pucarelli I, Segni M, Mancini MA, Troiani S. 1996 Combined treatment with gonadotropin-releasing hormone analog and growth hormone in central precocious puberty. *J Clin Endocrinol Metab.* 81:948–951.
23. Balducci R, Toscano V, Mangiantini A, et al. 1995 Adult height in short normal adolescent girls treated with GnRH α and GH. *J Clin Endocrinol Metab.* 80:3596–3600.
24. Cassorla F, Mericq V, Eggers M, et al. 1997 Effects of luteinizing hormone-releasing hormone analog-induced pubertal delay in growth hormone (GH)-deficient children treated with GH: preliminary results. *J Clin Endocrinol Metab.* 82:3989–3992.
25. Adan L, Souberbielle JC, Zucker JM, Pierre-Kahn A, Kalifa C, Brauner R. 1997 Adult height in 24 patients treated for GH deficiency and early puberty. *J Clin Endocrinol Metab.* 82:229–233.
26. Lanes R, Gunczler P. 1998 Final height after combined growth hormone and gonadotropin-releasing hormone analogue therapy in short healthy children entering into normally timed puberty. *Clin Endocrinol (Oxf).* 49:197–202.
27. Cara JF, Kreiter ML, Rosenfield RL. 1992 Height prognosis of children with true precocious puberty and growth hormone deficiency: effect of combination therapy with gonadotropin releasing hormone agonist and growth hormone. *J Pediatr.* 120:709–715.
28. Furlanetto RW, Marino JM. 1987 Radioimmunoassay of somatomedin C/insulin-like growth factor I. *Methods Enzymol.* 146:216–226.
29. Greulich W, Pyle SI. 1959 Radiographic atlas of skeletal development of the hand and wrist. Stanford: Stanford University Press.
30. Carter DR, Bouxsein ML, Marcus R. 1992 New approaches for interpreting projected bone densitometry data. *J Bone Miner Res.* 7:137–145.
31. Katzman DK, Bachrach LK, Carter DR, Marcus R. 1991 Clinical and anthropometric correlates of bone mineral acquisition in healthy adolescent girls. *J Clin Endocrinol Metab.* 73:1332–1339.
32. Stanhope R, Uruena M, Hindmarsh P, Leiper AD, Brook CGD. 1991 Management of growth hormone deficiency through puberty. *Acta Paediatr Scand.* 372(Suppl):47–52.
33. Stanhope R, Albanese A, Hindmarsh P, Brook CGD. 1992 The effects of growth hormone therapy on spontaneous sexual development. *Horm Res.* 38(Suppl 1):9–13.
34. Chan JM, Stampfer MJ, Giovannucci E, et al. 1998 Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science.* 279:563–566.
35. Pollak M. 1998 IGF-I physiology and breast cancer. *Recent Results Cancer Res.* 152:63–70.
36. Ma J, Pollak MN, Giovannucci E, et al. 1999 Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst.* 91:620–625.
37. Saggese G, Baroncelli GI, Bertelloni S, Barsanti S. 1996 The effect of long-term growth hormone (GH) treatment on bone mineral density in children with GH deficiency. Role of GH in the attainment of peak bone mass. *J Clin Endocrinol Metab.* 81:3077–3083.
38. Vance ML, Mauras N. 1999 GH therapy in adults and children. *N Engl J Med.* 341:1206–1216.