

Effect of Growth Hormone Dose on Bone Maturation and Puberty in Children with Idiopathic Short Stature

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Context: GH at 0.22 mg/kg-wk has been shown to have no effect on pubertal onset or pace, whereas GH at 0.5 mg/kg-wk has been shown to advance pubertal onset and bone maturation.

Objectives: Our objectives were to determine whether 0.37 mg/kg-wk GH advanced pubertal onset, pace, or bone maturation relative to 0.24 mg/kg-wk GH; whether 0.37 mg/kg-wk GH led to pubertal onset at an inappropriately early age; and whether age at start of GH therapy influenced pubertal onset.

Design: We conducted a randomized, open-label study to final height.

Patients: We studied children with idiopathic short stature.

Intervention: Patients were treated with 0.24 mg/kg-wk, 0.24 increasing to 0.37 mg/kg-wk, or 0.37 mg/kg-wk.

Main Outcome Measures: We assessed age at pubertal onset and

rates of bone maturation, Tanner stage development, and increase in testicular volume (boys only).

Results: For the primary comparison between the 0.24 and 0.37 mg/kg-wk dose groups, median ages of pubertal onset (in years) were similar (13.7 *vs.* 13.5 for boys and 11.7 *vs.* 11.4 for girls) and were greater than those for the general population for each sex. Age at start of GH therapy did not appear to influence pubertal onset for either sex. Rates of pubertal pace and bone maturation were not significantly different between the 0.24 and 0.37 mg/kg-wk dose groups for either sex.

Conclusion: GH at 0.37 mg/kg-wk does not appear to accelerate pubertal onset, pace, or bone maturation compared with GH at 0.24 mg/kg-wk in patients with idiopathic short stature. From a clinical standpoint, our results suggest that the approved dose range of up to 0.37 mg/kg-wk GH does not lead to pubertal onset at an inappropriately early age. (*J Clin Endocrinol Metab* 91: 169–175, 2006)

G H-IGF-I AXIS disorders have established a clear link between GH activity and pubertal timing. Before GH treatment became available, marked delays in pubertal onset were observed in children with isolated GH deficiency (1). Additionally, pubertal delays of 3–7 yr are observed in children with GH insensitivity (2).

Randomized controlled studies of recombinant human GH (somatropin) treatment of patients with idiopathic short stature (ISS) have yielded differing results regarding the influence of GH on pubertal onset, pubertal pace, and bone maturation. Although Leschek *et al.* (3) demonstrated no effect on pubertal onset or pace in boys who began low-dose (0.22 mg/kg-wk) GH at a mean age of 12 yr, Kamp *et al.* (4) demonstrated acceleration of pubertal onset and bone maturation by approximately 1 yr in boys and girls who began high-dose (0.5 mg/kg-wk) GH at a mean age of 8 yr. These results suggest that the influence of GH on pubertal timing and bone maturation may be dose-dependent. Thus, based on the current literature, decisions regarding GH dosing are limited by uncertainty as to which doses between 0.22 and

0.5 mg/kg-wk might accelerate puberty and bone maturation in patients with ISS.

We tested the influence of GH dose on pubertal onset, pubertal pace, and bone maturation during a randomized, open-label study to final height in patients with ISS (mean age, 9.8 yr) randomized to one of three GH dose groups (5, 6). We assessed 1) whether the higher dose (0.37 mg/kg-wk) advanced pubertal timing and bone maturation relative to the lower dose (0.24 mg/kg-wk); 2) whether the higher dose led to pubertal onset at an age younger than that reported for the general population (7–11); and 3) whether age at start of GH therapy influenced pubertal onset in the higher *vs.* lower dose group.

GH dose effects on height velocity, height SD score (SDS), and final height have been reported for patients in this study (6, 12, 13), as have safety data (13, 14). Studies of pubertal timing and growth (15), immunological function (16), and quality of life (17) have been reported for subsets of these patients. The primary efficacy manuscript for this study included a statement, without data, regarding the influence of GH dose on puberty and bone maturation (6). Here, we present data and rigorous statistical analyses showing that 0.37 mg/kg-wk GH does not appear to accelerate pubertal onset, pubertal pace, or bone maturation compared with 0.24 mg/kg-wk GH, or lead to pubertal onset at an inappropriately early age (7–11), in patients with ISS.

First Published Online November 1, 2005

Abbreviations: BA, Bone age; CA, chronological age; CI, confidence interval; ISS, idiopathic short stature; LS, least-squares; SDS, SD score; TS, Tanner stage; TV, testicular volume; TW2, Tanner-Whitehouse.

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Patients and Methods

Patients

The study, initiated in 1987, enrolled 239 children from 28 centers in Austria, Finland, France, Germany, Greece, Israel, Netherlands, Norway, Spain, and United Kingdom. Inclusion criteria were chronological age (CA) of at least 5 yr, bone age (BA) less than 12 yr (boys) or less than 10 yr (girls) (18), pubertal development at Tanner stage 1 (TS1) (7, 8), height at least 2 sd below the mean for age (19), height velocity below the 25th percentile for CA before 12 yr of age (boys) or 10 yr of age (girls), or below the 25th percentile for BA beyond these ages (19), normal or adequately controlled thyroid function, and peak stimulated GH greater than 20 mU/liter (approximately 10 μ g/liter) in a standard stimulation test. Exclusion criteria included current or prior treatment with GH, organic cause of growth failure, primary bone disease, endocrine or metabolic disorder, or dysmorphic syndrome. Children born small for gestational age ($n = 33$) were not excluded.

Study design

The study was conducted in accordance with the principles of the Declaration of Helsinki. An institutional review board approved study conduct at each center, and investigators obtained informed consent before conducting any study-related procedure.

The study consisted of screening; a 2-yr, three-arm, randomized, open-label, parallel, dose-response, height velocity phase; and an extension phase to final height. At screening, a patient history was recorded, TS was assessed, and diagnostic tests (including a standard GH stimulation test and a BA x-ray) were performed to establish study eligibility. No more than 12 months later, eligible patients attended the first study visit, at which TS was reassessed, baseline data were recorded, and patients received their first dose of GH (Humatrope; Eli Lilly and Co., Indianapolis, IN) [0.24 mg/kg-wk ($n = 49$ boys and 29 girls), 0.24 mg/kg-wk for 1 yr and 0.37 mg/kg-wk thereafter (0.24→0.37 mg/kg-wk; $n = 50$ boys and 28 girls), or 0.37 mg/kg-wk ($n = 59$ boys and 24 girls)]. GH was administered sc in divided doses six times weekly throughout the study.

Pubertal measurements

Pubertal staging was evaluated every 3 months and BA every 6 months during the dose-response phase of the study. Pubertal staging and BA were evaluated every 12 months during the extension phase of the study. Pubertal onset was defined as TS2 development (breast for girls; genital for boys) (7, 8). BA was determined by a central reader [Les Cox, Ph.D., Lecturer in Human Biology (retired), The Biochemistry, Endocrinology, and Metabolism Unit, Institute of Child Health, London, UK] using the Tanner-Whitehouse (TW2) method (18). To enable determination of Bayley-Pinneau predicted heights, TW2 BA were converted to Greulich-Pyle BA in boys (Greulich-Pyle = $0.9945 \times TW2 - 0.5560$; $r^2 = 0.997$) and girls (Greulich-Pyle = $0.9873 \times TW2 - 0.4377$; $r^2 = 0.993$) (20). Greulich-Pyle BA were used in all BA analyses. Testicular volume (TV) was determined by comparison with an orchidometer (21).

Data analysis

Baseline data are reported for all dose groups. Because the comparison between the 0.24 and 0.37 mg/kg-wk dose groups was considered primary, unless otherwise specified, P values are based on a comparison between these two dose groups.

Pubertal onset was analyzed for 1) all patients who were prepubertal at start of GH therapy [$n = 156$ boys and 79 girls; four of the 239 randomized patients were excluded from this analysis either because they had entered puberty between screening and start of GH therapy ($n = 3$) or because they had no on-study TS data available ($n = 1$)]; and 2) a young cohort of these patients whose study entry ages (in years) were similar to those in Kamp *et al.* (4) [our study: boys, 5–10 ($n = 65$), and girls, 5–8 ($n = 25$); Kamp *et al.*: boys, 4–10, and girls, 4–8]. Age at study entry was the only criterion that differentiated the young cohort from the group of patients studied for pubertal onset as a whole.

In both populations, age at pubertal onset and time on GH therapy to pubertal onset were analyzed for each sex separately, using survival

analysis methods. Age at pubertal onset was defined as the patient's age at the visit at which he or she first showed TS2 development, whereas time on GH therapy to pubertal onset was defined as the interval between the visit at which GH therapy was started and the visit at which the patient first showed TS2 development.

For all patients who were prepubertal at start of GH therapy, Kaplan-Meier methods were used to assess pubertal onset; tests of equality of survival curves were performed by the log-rank test, and results are presented as medians with 95% confidence intervals (CI).

For boys in the young cohort, there were baseline imbalances for BA and height SDS. Therefore, Cox proportional hazards methods that included baseline BA and baseline height SDS as covariates were used to analyze this group. For clarity of presentation, the same methods were used to analyze girls in the young cohort. Tests of equality of hazard functions between the 0.24 and 0.37 mg/kg-wk dose groups were performed with χ^2 tests and are presented as estimated hazard ratios with P values. Hazard ratios indicate the relative risk of entering puberty at any given point in time for patients receiving 0.37 vs. 0.24 mg/kg-wk GH; a hazard ratio of 1 indicates identical risk between dose groups, whereas a hazard ratio greater than 1 indicates that patients receiving 0.37 mg/kg-wk are at a greater instantaneous risk. Survival curves, adjusted for mean baseline BA and mean baseline height SDS separately for each sex, were generated to estimate the median age at pubertal onset and the median time on GH therapy to pubertal onset for the young cohort.

Analyses of pubertal pace and bone maturation include data from the first 4 yr after pubertal onset. Patients were included in these analyses if they reached puberty after screening and had all the necessary covariate information for the statistical model ($n = 114$ boys and 62 girls). Pubertal pace and bone maturation were assessed by repeated-measures analyses. Correlation between observations on the same patient was assumed to decline with increase in time difference between the observations. Response variables assessed were BA, TS, and TV (boys only). The models included terms for age at pubertal onset and initial BA deficit. Age at visit was the repeated-measures parameter.

Kaplan-Meier methods were used to analyze duration of puberty (*i.e.* the interval between the visit at which the patient first showed TS2 development and the visit at which the patient first showed TS5 development) separately for each sex. Patients were included if they reached puberty after screening ($n = 114$ boys and 64 girls).

For the analysis of final TV (*i.e.* the last available TV measured after the patient showed TS5 development), boys were included if they were on study throughout puberty ($n = 56$). Simple summary statistics (mean \pm sd) are provided for this analysis. Kaplan-Meier methods were used to analyze age at achievement of TV of at least 15 ml for all boys who were prepubertal at start of GH therapy ($n = 156$).

Descriptive statistics were used to summarize baseline characteristics for all patients. Results are expressed as means \pm sd for actual measured values and as least-squares (LS) means \pm se for LS means from repeated-measures models.

Results

Baseline data

Baseline characteristics for all randomized patients and for those who reached puberty after screening did not differ significantly among the three dose groups for either sex (Table 1). For the young cohort, there were no significant differences in baseline characteristics among the three dose groups for either sex, except for baseline height SDS ($P = 0.02$ for all doses) and baseline BA ($P = 0.01$ for all doses) in boys (Table 1).

Follow-up of patients

Of all randomized patients (excluding one for whom no on-study TS data were available), 43 boys and 17 girls discontinued before pubertal onset at TS2, whereas 56 boys and 19 girls reached TS5 on study (Table 2).

TABLE 1. Baseline characteristics of all randomized patients, patients who reached puberty after screening, and the young cohort with an age range similar to that in Kamp *et al.* (4)

| GH dose (mg/kg-wk) | All randomized patients | | | Patients who reached puberty after screening | | | Young cohort with age range similar to that in Kamp <i>et al.</i> (4) | | |
|----------------------------|-------------------------|-------------|------------|--|-------------|------------|---|-------------|------------|
| | 0.24 | 0.24 → 0.37 | 0.37 | 0.24 | 0.24 → 0.37 | 0.37 | 0.24 | 0.24 → 0.37 | 0.37 |
| Boys | | | | | | | | | |
| n | 49 | 50 | 59 | 38 | 32 | 44 | 19 | 20 | 26 |
| Age (yr) | 10.1 ± 2.5 | 10.3 ± 2.2 | 10.3 ± 2.2 | 10.4 ± 2.5 | 10.7 ± 2.0 | 10.6 ± 2.1 | 7.4 ± 1.6 | 8.0 ± 1.6 | 8.3 ± 1.2 |
| Height SDS | -3.2 ± 0.7 | -3.0 ± 0.6 | -3.0 ± 0.4 | -3.2 ± 0.7 | -3.0 ± 0.6 | -2.9 ± 0.4 | -3.6 ± 0.8 | -3.1 ± 0.6 | -3.0 ± 0.5 |
| BA (yr) | 8.0 ± 2.6 | 8.3 ± 2.1 | 8.3 ± 1.9 | 8.4 ± 2.5 | 8.5 ± 1.9 | 8.5 ± 1.7 | 5.4 ± 1.6 | 6.4 ± 1.6 | 6.9 ± 1.4 |
| BA delay (yr) | 1.9 ± 1.2 | 1.7 ± 1.1 | 1.7 ± 1.4 | 1.9 ± 1.3 | 1.9 ± 1.0 | 1.8 ± 1.5 | 1.7 ± 1.1 | 1.3 ± 0.9 | 1.0 ± 0.9 |
| BMI (kg/m ²) | 15.4 ± 1.7 | 15.6 ± 1.6 | 15.7 ± 1.4 | 15.4 ± 1.9 | 15.9 ± 1.6 | 15.8 ± 1.5 | 15.1 ± 1.3 | 14.8 ± 1.4 | 15.3 ± 1.4 |
| Girls | | | | | | | | | |
| n | 29 | 28 | 24 | 20 | 24 | 20 | 10 | 7 | 8 |
| Age (yr) | 8.3 ± 1.7 | 9.2 ± 1.9 | 9.0 ± 2.1 | 8.3 ± 1.6 | 9.1 ± 2.0 | 9.4 ± 2.1 | 6.4 ± 0.8 | 6.3 ± 0.6 | 6.5 ± 0.8 |
| Height SDS | -3.6 ± 0.9 | -3.6 ± 0.7 | -3.2 ± 0.8 | -3.7 ± 1.0 | -3.6 ± 0.7 | -3.1 ± 0.6 | -4.3 ± 1.1 | -4.1 ± 1.0 | -3.4 ± 0.9 |
| BA (yr) ^a | 6.3 ± 2.2 | 7.6 ± 2.6 | 7.1 ± 2.2 | 6.6 ± 2.2 | 7.6 ± 2.6 | 7.5 ± 1.8 | 4.5 ± 1.5 | 4.2 ± 1.8 | 4.9 ± 2.0 |
| BA delay (yr) ^a | 1.5 ± 1.3 | 1.3 ± 1.4 | 1.6 ± 1.3 | 1.1 ± 1.3 | 1.3 ± 1.3 | 1.8 ± 1.1 | 1.5 ± 1.1 | 1.8 ± 1.6 | 1.3 ± 1.5 |
| BMI (kg/m ²) | 15.1 ± 1.9 | 15.1 ± 1.7 | 14.6 ± 1.9 | 15.2 ± 2.2 | 15.1 ± 1.8 | 14.6 ± 2.0 | 13.9 ± 1.1 | 13.7 ± 1.9 | 13.4 ± 1.3 |

Except for patient numbers, data are means ± SD. BA is according to Greulich and Pyle (20). BMI, Body mass index.

^a BA and BA delays were measured in 28 of 29 girls in the 0.24 mg/kg-wk GH dose group and 23 of 24 girls in the 0.37 mg/kg-wk GH dose group for all randomized patients; in 19 of 20 girls in the 0.24 mg/kg-wk GH dose group and 19 of 20 girls in the 0.37 mg/kg-wk GH dose group for patients who reached puberty after screening; and in seven of eight girls in the 0.37 mg/kg-wk GH dose group for the young cohort.

Treatment duration

Treatment duration and age at last height assessment (in years) were 4.6 ± 2.4 and 14.5 ± 3.0 , respectively (patients who were prepubertal at start of GH therapy; $n = 235$); 5.3 ± 2.0 and 15.6 ± 2.3 , respectively (patients who reached puberty after screening; $n = 178$); and 5.5 ± 2.8 and 13.1 ± 3.2 , respectively (patients in the young cohort; $n = 90$).

Pubertal onset

Seventy-seven percent (37 of 48) of boys receiving 0.24 mg/kg-wk GH entered puberty during the study, compared with 64% (32 of 50) of boys receiving 0.24→0.37 mg/kg-wk GH and 76% (44 of 58) of boys receiving 0.37 mg/kg-wk GH. Sixty-nine percent (20 of 29) of girls receiving 0.24 mg/kg-wk GH entered puberty during the study, compared with 85% (23 of 27) of girls receiving 0.24→0.37 mg/kg-wk GH and 83% (19 of 23) of girls receiving 0.37 mg/kg-wk GH.

The median time on GH therapy to pubertal onset (in years) was not significantly different between the 0.24 and 0.37 mg/kg-wk dose groups for either boys [3.0 (95% CI, 3.0–4.9) vs. 3.0 (95% CI, 1.8–3.2), respectively; $P = 0.2$] or girls [3.0 (95% CI, 3.0–4.0) vs. 2.0 (95% CI, 1.1–4.0), respectively; $P = 0.2$]. Similarly, in the young cohort, the estimated hazard ratio for time on GH therapy to pubertal onset was not significantly different between the 0.24 and 0.37 mg/kg-wk dose groups for either boys (0.9; $P = 0.9$) or girls (1.1; $P = 0.9$). In the young cohort, the adjusted median time on GH therapy to pubertal onset (in years) was 5.0 for both dose groups for boys and 4.0 for both dose groups for girls.

Of all patients who were prepubertal at start of GH therapy, the percentage remaining prepubertal at each age (from 9–16 yr in boys and 9–14 yr in girls) was similar among the three dose groups (Fig. 1, A and B). The median ages of pubertal onset during the study (in years) were not significantly different between the 0.24 and 0.37 mg/kg-wk dose groups for boys [13.7 (95% CI, 13.3–14.3) vs. 13.5 (95% CI, 13.0–14.1), respectively; $P = 0.2$] or girls [11.7 (95% CI, 10.9–

12.0) vs. 11.4 (95% CI, 11.0–11.8), respectively; $P = 0.8$], and were greater than those for the general population for each sex (7–11).

Similarly, in the young cohort, the estimated hazard ratio for age at pubertal onset was not significantly different between the 0.24 and 0.37 mg/kg-wk dose groups for boys (1.3; $P = 0.6$) or girls (1.0; $P = 1.0$). In the young cohort, the adjusted median ages of pubertal onset (in years) were 12.7 and 12.3 for boys in the 0.24 and 0.37 mg/kg-wk dose groups, respectively; the adjusted median age of pubertal onset (in years) was 11.0 for both dose groups for girls.

Pubertal pace

TS. Rates of TS progression after pubertal onset were similar across all dose groups in both sexes ($P = 0.9$ for all doses for boys and $P = 0.7$ for all doses for girls) (Fig. 2, A and C). The median duration of puberty (in years) was 3.0 (95% CI, 3.0–3.3) for boys and 3.5 (95% CI, 3.0–5.3) for girls.

TV. Rates of increase of TV after pubertal onset were similar across all dose groups ($P = 0.7$ for all doses) (Fig. 2B). GH dose had no effect on the LS mean (\pm SE) rate of increase of TV (in ml/yr) between the 0.24 and 0.37 mg/kg-wk dose groups (3.5 ± 0.3 vs. 3.6 ± 0.3 , respectively; $P = 0.9$). TV of at least 15 ml, the estimated critical volume required for normal adult testicular function (22–24), was achieved at a median age (in years) of 16.7 (95% CI, 15.5–17.2) in boys receiving 0.24 mg/kg-wk GH vs. 15.6 (95% CI, 15.0–16.2) in boys receiving 0.37 mg/kg-wk GH. In boys who were on study throughout puberty, there was no significant difference between the 0.24 and 0.37 mg/kg-wk dose groups in final TV (in ml) (17.7 ± 5.0 vs. 16.9 ± 5.4 , respectively; $P = 0.7$).

Bone maturation

Rates of bone maturation after pubertal onset were similar across dose groups ($P = 0.8$ for all doses for boys and $P =$

TABLE 2. Frequencies of the maximum TS recorded for all randomized patients^a

| | No. of patients ^b on each GH dose (mg/kg-wk) | | | Total |
|----------------------|---|-------------|------|-------|
| | 0.24 | 0.24 → 0.37 | 0.37 | |
| TS in boys (genital) | | | | |
| 1 | 11 | 18 | 14 | 43 |
| 2 | 4 | 7 | 3 | 14 |
| 3 | 8 | 2 | 9 | 19 |
| 4 | 9 | 9 | 7 | 25 |
| 5 | 17 | 14 | 25 | 56 |
| TS in girls (breast) | | | | |
| 1 | 9 | 4 | 4 | 17 |
| 2 | 5 | 1 | 4 | 10 |
| 3 | 2 | 9 | 3 | 14 |
| 4 | 7 | 6 | 8 | 21 |
| 5 | 6 | 8 | 5 | 19 |

Study discontinuations either before pubertal onset (*i.e.* before reaching TS2) or before completion of puberty (*i.e.* before reaching TS5) were unlikely to have influenced our conclusions, because there was no evidence, based on investigators' records documenting the reasons for study discontinuation, that any patient discontinued because of concerns of abnormal pubertal development. Thus, the key assumptions regarding missing data (necessary for the validity of the statistical inferences) appear to have been met, and so the Kaplan-Meier, Cox proportional hazards, and repeated-measures analyses that we performed appropriately took these missing data into account. To further test the robustness of our results, we performed a Kaplan-Meier analysis in which patients who discontinued before pubertal onset were considered to have achieved puberty at their next scheduled visit. Although age at pubertal onset (in years) was earlier by 0.3–0.5 yr based on this analysis [13.4 (95% CI, 12.9–13.9) *vs.* 13.0 (95% CI, 12.7–13.6) for boys in the 0.24 and 0.37 mg/kg-wk dose groups, respectively, $P = 0.23$; and 11.2 (95% CI, 10.7–11.7) *vs.* 11.1 (95% CI, 10.8–11.7) for girls in the 0.24 and 0.37 mg/kg-wk dose groups, respectively, $P = 0.97$], our conclusion that there was no significant difference between the 0.24 and 0.37 mg/kg-wk dose groups remained unchanged.

^a Excludes one patient who had no on-study TS data available.

^b Three patients included here were excluded from pubertal onset analysis because they had entered puberty between screening and start of GH therapy: 0.24 mg/kg-wk ($n = 1$ boy), 0.24 → 0.37 mg/kg-wk ($n = 1$ girl), and 0.37 mg/kg-wk ($n = 1$ girl).

0.7 for all doses for girls) (Fig. 3, A and B) and were not significantly different between the 0.24 and 0.37 mg/kg-wk dose groups for either sex. LS mean (\pm SE) rates of bone maturation (in bone years per chronological year) were 1.0 ± 0.07 *vs.* 1.0 ± 0.06 for boys ($P = 0.6$) and 0.9 ± 0.09 *vs.* 0.9 ± 0.09 for girls ($P = 0.9$) in the 0.24 and 0.37 mg/kg-wk dose groups, respectively.

Children born small for gestational age

The above analyses yielded similar results after exclusion of children born small for gestational age ($n = 33$); no statistically significant differences were observed between or among doses for pubertal onset, pubertal pace, or bone maturation (data not shown).

Discussion

This open-label, randomized, dose-response study shows that the approved GH dose of 0.37 mg/kg-wk does not appear to accelerate pubertal onset, pubertal pace, or bone maturation compared with the GH dose of 0.24 mg/kg-wk, or lead to pubertal onset at an inappropriately early age

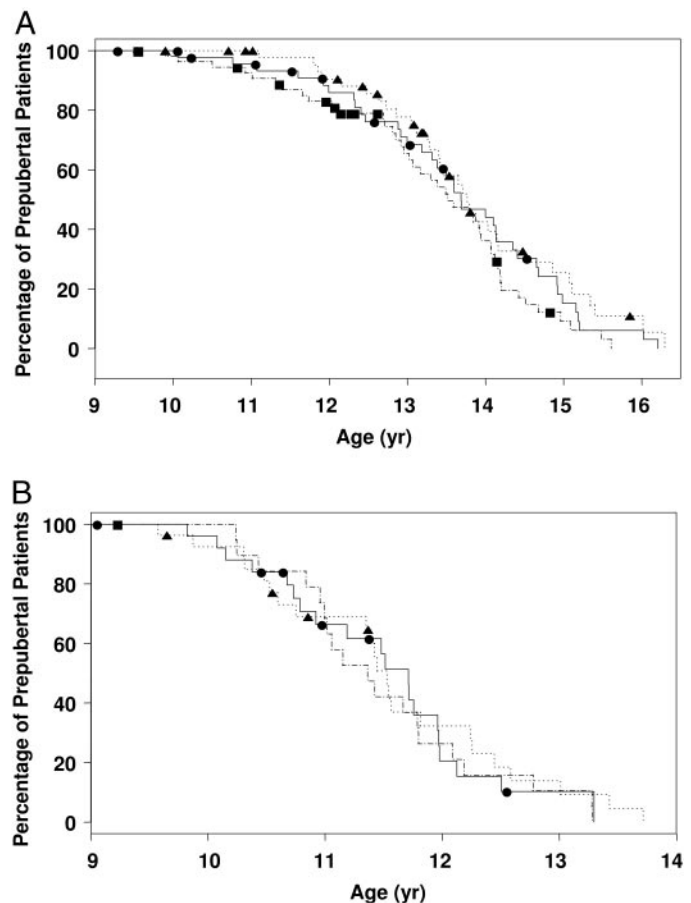


FIG. 1. A, Kaplan-Meier plot of pubertal onset in all randomized boys who were prepubertal at start of GH therapy. *Solid line*, 0.24 mg/kg-wk GH; *dotted line*, 0.24 → 0.37 mg/kg-wk GH; *broken line with dots*, 0.37 mg/kg-wk GH. ●, ▲, and ■ indicate patients who discontinued before reaching puberty. B, Kaplan-Meier plot of pubertal onset in all randomized girls who were prepubertal at start of GH therapy. *Solid line*, 0.24 mg/kg-wk GH; *dotted line*, 0.24 → 0.37 mg/kg-wk GH; *broken line with dots*, 0.37 mg/kg-wk GH. ●, ▲, and ■ indicate patients who discontinued before reaching puberty.

(7–11), in patients with ISS who began treatment prepubertally at a mean age of 9.8 yr.

This study has potential limitations. First, there was no untreated control group, and thus we cannot exclude the possibility of a change in pubertal timing or bone maturation relative to untreated controls. However, comparison of our data with normative standards (7–11) suggests that pubertal onset in our patients was appropriate relative to the general population. Complicating this interpretation, however, is the fact that prepubertal patients joined the study at various ages. For prepubertal patients who entered the study at younger ages, there was a broad age range during which they entered puberty after beginning GH therapy. For prepubertal patients who entered the study at older ages, however, the age range for entering puberty was narrower, necessarily excluding ages younger than those at which the patients began therapy. This truncation effect may have skewed the median ages of pubertal onset toward older ages. Nevertheless, restricting the analysis to the young cohort did not alter the conclusion that the median ages of pubertal onset were

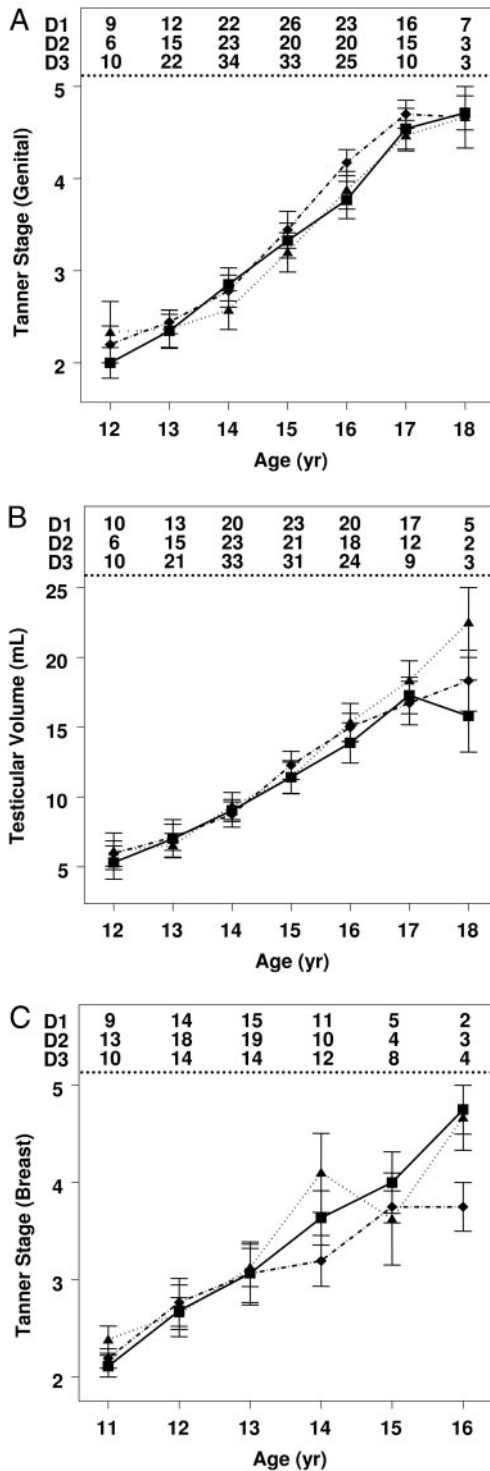


FIG. 2. A, TS (genital) vs. CA in boys who reached puberty after screening. ■, 0.24 mg/kg-wk GH (D1); ▲, 0.24→0.37 mg/kg-wk GH (D2); ◆, 0.37 mg/kg-wk GH (D3). The number of patients at each age is indicated for each dose group. Results are means ± SE. B, TV vs. CA in boys who reached puberty after screening. ■, 0.24 mg/kg-wk GH (D1); ▲, 0.24→0.37 mg/kg-wk GH (D2); ◆, 0.37 mg/kg-wk GH (D3). The number of patients at each age is indicated for each dose group. Results are means ± SE. C, TS (breast) vs. CA in girls who reached puberty after screening. ■, 0.24 mg/kg-wk GH (D1); ▲, 0.24→0.37 mg/kg-wk GH (D2); ◆, 0.37 mg/kg-wk GH (D3). The number of patients at each age is indicated for each dose group. Results are means ± SE.

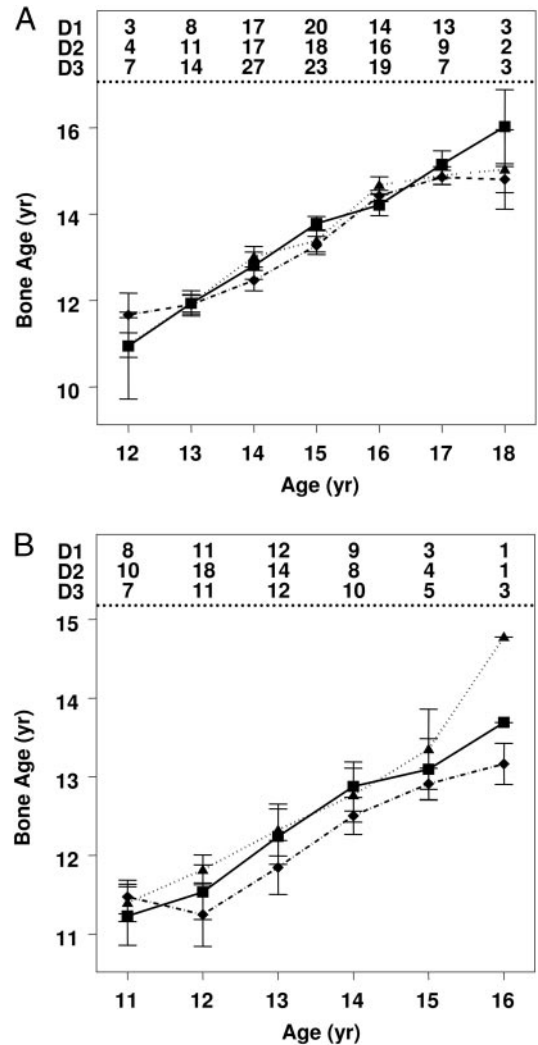


FIG. 3. A, BA vs. CA in boys who reached puberty after screening. ■, 0.24 mg/kg-wk GH (D1); ▲, 0.24→0.37 mg/kg-wk GH (D2); ◆, 0.37 mg/kg-wk GH (D3). The number of patients at each age is indicated for each dose group. Results are means ± SE. B, BA vs. CA in girls who reached puberty after screening. ■, 0.24 mg/kg-wk GH (D1); ▲, 0.24→0.37 mg/kg-wk GH (D2); ◆, 0.37 mg/kg-wk GH (D3). The number of patients at each age is indicated for each dose group. Results are means ± SE.

normal, without dose-related effects. Additionally, because all patients were prepubertal at study entry, a truncation effect on the median age of pubertal onset would not affect the conclusion that there was no dose effect on pubertal onset.

Second, the interval between visits (1 yr) during the extension phase of our study (*i.e.* the phase during which most patients entered puberty) was longer than in some other studies. Compared with studies with a visit interval of 3 months, such as those by Marshall and Tanner (7, 8), this difference in study design would be expected to add up to 0.4 yr to the median age of pubertal onset due to the greater delay in ascertainment. However, this design feature would not alter our conclusions that there was no dose effect on pubertal onset and that pubertal onset was appropriate relative to the general population.

Third, we cannot exclude the possibility that type II error

(*i.e.* finding no significant result when in fact there is a true underlying effect) may have led to our observation that pubertal timing was not accelerated. Although this study was not powered for the secondary endpoints reported herein, a retrospective analysis indicated that an observed difference in median pubertal onset ages of approximately 0.4 and 1.1 yr in boys and girls, respectively, could have been detected with $P < 0.05$.

Results with the lower GH dose used in our study (0.24 mg/kg·wk) were similar to those of Leschek *et al.* (3), who observed no acceleration of pubertal onset or pace compared with placebo-treated controls in patients who began low-dose (0.22 mg/kg·wk) GH at a mean age of 12 yr. Because our lower dose was similar to that used by Leschek *et al.* (3), it is unlikely that acceleration of puberty and bone maturation had plateaued at the lower dose in our study (which would have rendered further acceleration undetectable at the higher dose of 0.37 mg/kg·wk GH). Our higher GH dose (0.37 mg/kg·wk) did not appear to advance bone maturation, with mean ratios of BA/CA less than or equal to 1 throughout the study. Importantly, our higher dose did not appear to lead to pubertal onset at an inappropriately early age (7–11).

Results in the literature differ with regard to the influence of GH on pubertal onset and pace. Some of these inconsistencies may be related to small sample size. The first randomized study compared only 10 GH-treated girls with a similar number of untreated controls (25), and more recent randomized controlled studies have included fewer than 20 patients per treatment group (3, 4). Differences in study design may also explain some of the observed inconsistencies regarding the influence of GH on pubertal onset and pace. Less rigorous studies, including those lacking concurrent controls, have demonstrated either no influence of GH on pubertal onset (15, 26) or pace (15, 27, 28) or, alternatively, acceleration of pubertal onset (29) or pace (26–29) in children with ISS.

Even randomized controlled studies, characterized as having more monitoring and experimental rigor than other study designs, have given differing results (3, 4). Kamp *et al.* (4) observed advancement of pubertal onset and bone maturation in patients who began high-dose (0.5 mg/kg·wk) GH at a mean age of 8 yr, whereas Leschek *et al.* (3) observed no such effect in patients who began low-dose (0.22 mg/kg·wk) GH at a mean age of 12 yr.

Our patients began treatment at an intermediary mean age of 9.8 yr. Kamp *et al.* (4) suggested that the young age at which their patients began GH therapy may have influenced the effect of GH on pubertal onset (4). However, data from a young cohort of our patients whose age range was similar to that in the study by Kamp *et al.* (4) showed no evidence of acceleration of pubertal onset for the 0.37 mg/kg·wk dose compared with the 0.24 mg/kg·wk dose. Thus, the higher GH dose used in the study by Kamp *et al.* (4) seems a more likely explanation for accelerated pubertal onset. Alternatively, type I error (*i.e.* finding a significant result when in fact there is no true underlying effect) may have led to the authors' observation of accelerated pubertal onset.

Using a lower dose of GH (0.37 mg/kg·wk) than that used by Kamp *et al.* (4), we observed ages at pubertal onset that were appropriate compared with the general population (7–

11), even in our young cohort. Moreover, we observed no dose-related effects on pubertal onset, pubertal pace, or bone maturation. Although dose-related effects may emerge at higher doses of GH, our results indicate that the dose of 0.37 mg/kg·wk may be used in patients with ISS (even those as young as 5 yr of age) without concern of accelerating puberty or bone maturation.

These results have clinical implications for GH dose selection in the treatment of patients with ISS, in that they resolve an ongoing safety concern regarding the use of higher doses of GH in this group. Although the dose responses for the influence of GH on growth, puberty, and adverse events have not been precisely defined, an optimal GH dose would maximize height gain without increasing adverse events, and would minimize the influence of GH on pubertal timing and bone maturation. As reported separately (6), the mean differences between final height and baseline predicted height were 7.2 and 5.4 cm for the 0.37 and 0.24 mg/kg·wk dose groups, respectively. Furthermore, 94 vs. 71% of final heights were within the normal range for the 0.37 and 0.24 mg/kg·wk dose groups, respectively. Because 0.37 mg/kg·wk GH led to a significantly greater final height gain than 0.24 mg/kg·wk GH (by 3.6 cm for patients with final height measurements, and by 2.8–3.5 cm for patients in the intent-to-treat analyses) (6) without accelerating pubertal timing or bone maturation, the more effective dose of 0.37 mg/kg·wk can be used in patients with ISS who are at least 5 yr of age with assurance that this dose will have no clinically important effect on pubertal onset, pubertal pace, or bone maturation.

Acknowledgments

We thank the principal investigators of the European Idiopathic Short Stature Study Group: C. Dacou-Voutetakis (Greece); H. Frisch, W. Stoegmann, and W. Tulzer (Austria); E. Leiberman (Israel); J.-C. Job, J.-L. Chaussain, F. Girard, R. Jean, M. L. A. Pierson, P. Chatelain, and M. Colle (France); U. Irlé, M. B. Ranke, O. Butenandt, H. P. Schwarz, R. Muehlenberg, H. J. Boehles, G. von Kalkreuth, and W. G. Sippell (Germany); R. de Yturriaga (Spain); M. A. Preece, J. M. H. Buckler, P. H. W. Rayner, and D. A. Price (United Kingdom); M.-L. Kaar and H. L. Lenko (Finland); and D. Aarskog (Norway). We also thank D. Cao, C. Konkoy, and J. Lin for their assistance in preparing the manuscript, and A. Attanasio for his help in conducting the study.

Received April 25, 2005. Accepted October 26, 2005.

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This work was supported by Eli Lilly and Co. and is based upon the results from protocol B9R-EW-E001.

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