Adult Height after Long-Term, Continuous Growth Hormone (GH) Treatment in Short Children Born Small for Gestational Age: Results of a Randomized, Double-Blind, Dose-Response GH Trial

YVONNE VAN PAREREN, PAUL MULDER, MIEKE HOUDIJK, MAARTEN JANSEN, MAARTEN REESER, AND ANITA HOKKEN-KOELEGA

Department of Pediatrics, Division of Endocrinology, Sophia Children's Hospital/Erasmus Medical Center (Y.v.P., A.H.-K.), 3015 GJ Rotterdam, The Netherlands; Department of Epidemiology and Biostatistics, Erasmus Medical Center (P.M.), 3015 GJ Rotterdam, The Netherlands; Academic Hospital of Free University (M.H.), 1081 HV Amsterdam, The Netherlands; Wilhelmina Children's Hospital (M.J.), 3584 EA Utrecht, The Netherlands; and Juliana Children's Hospital (M.R.), 2566 MJ The Hague, The Netherlands

The GH dose-response effect of long-term continuous GH treatment on adult height (AH) was evaluated in 54 short children born small for gestational age (SGA) who were participating in a randomized, double-blind, dose-response trial. Patients were randomly and blindly assigned to treatment with either 3 IU (group A) or 6 IU (group B) GH/m²·d (~0.033 or 0.067 mg/kg·d, respectively). The mean (±SD) birth length was −3.6 (1.4), the age at the start of the study was 8.1 (1.9) yr, and the height SD score (SDS) at the start of the study −3.0 (0.7). Seventeen of the 54 children were partially GH deficient (stimulated GH peak, 10–20 mU/liter). Fifteen non-GH-treated, non-GH-deficient, short children born SGA, with similar inclusion criteria, served as controls [mean (±SD) birth length, −3.3 (1.2); age at start, 7.8 (1.7) yr; height SDS at start, −2.6 (0.5)]. GH treatment resulted in an AH above −2 SDS in 85% of the children after a mean (±SD) GH treatment period of 7.8 (1.7) yr. The mean (SD) AH SDS was −1.1 (0.7) for group A and −0.9 (0.8) for group B, resulting from a mean (±SD) gain in height SDS of 1.8 (0.7) for group A and 2.1 (0.8) for group B. No significant differences between groups A and B were found for AH SDS (mean difference, 0.3 SDS; 95% confidence interval, −0.2, 0.6; P > 0.2) and gain in height SDS (mean difference, 0.3 SDS; 95% confidence interval, −0.1, 0.7; P > 0.1). When corrected for target height, the mean corrected AH SDS was −0.2 (0.8) for group A and −0.4 (0.9) for group B. The mean (±SD) AH SDS of the control group [−2.3 (0.7)] was significantly lower than that of the GH-treated group (P < 0.001). Multiple regression analysis indicated the following predictive variables for AH SDS: target height SDS, height SDS, and chronological age minus bone age (years) at the start of the study. GH dose had no significant effect. In conclusion, long-term continuous GH treatment in short children born SGA without signs of persistent catch-up growth leads to a normalization of AH, even with a GH dose of 3 IU/m²·d (~0.033 mg/kg·d). (*J Clin Endocrinol Metab* 88: 3584–3590, 2003)

TO BE BORN small for gestational age (SGA) may have considerable consequences. Not only has a significantly increased risk for reaching an adult height (AH) below −2 SD score (SDS) been reported (1), but there might also be an increased risk for diabetes mellitus type 2 and cardiovascular disease, as has been described in adults with a low birth weight (2). It is as yet unclear whether this will also be true for SGA patients with persistent short stature, as no distinction was made for those who had complete catch-up growth in height after birth and those with persistent short stature.

During the first 2 yr of life, about 15% of the children born SGA do not catch-up to a height above −2 SDS. The majority of these children will reach an AH below −2 SDS (2, 3). The reason for these children remaining short is not completely understood. Sixty percent of short children born SGA have low serum GH levels during a 24-h GH profile, but no relation was found between physiological GH levels and the growth response during GH treatment (4–6). There are sev-

eral theories to explain their persistent short stature. One suggests that it is the result of a reduced sensitivity for growth factors; another suggests that it might be influenced by intrauterine reprogramming or genetic background (7–9). Recent studies have demonstrated that 5 yr of GH treatment in short children born SGA results in a normalization of height during childhood (6, 10). AH results after long-term, continuous GH treatment, however, have not yet been published.

In this article we present AH results of 54 short children born SGA who were treated in a randomized, double-blind, dose-response GH trial evaluating the efficacy and safety of long-term, continuous GH treatment with either 3 or 6 IU GH/m²·d (0.033 or 0.067 mg/kg·d).

Subjects and Methods

Study group

Seventy-nine prepubertal short children born SGA participated in a multicenter, double-blind, randomized, dose-response GH trial. Of these 79 children, six children dropped out of the study for the following reasons: lack of motivation despite ongoing catch-up growth (n = 4), treatment for precocious puberty (n = 1), and biochemical signs of GH insensitivity (n = 1). As these six children were lost to follow-up, their

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Abbreviations: AH, Adult height; ATT, arginine tolerance test; BA, bone age; BMI, body mass index; CA, chronological age; CI, confidence interval; GHD, GH deficiency; HV, height velocity; PI, prediction interval; SDS, SD score; SGA, small for gestational age; TH, target height.

data were not included in the analysis. Of the remaining 73 children, 54 children reached AH, and their data were evaluated for this study, whereas 19 children were not included because they had not yet reached AH. Those who had attained AH were approximately 3 yr older at the start of GH treatment compared with those who were still growing [mean (±SD) chronological age (CA), 8.1 (1.9) *vs.* 5.4 (1.9) yr; $P < 0.001$], but the other clinical characteristics were similar at the start of GH treatment (Table 1).

The dose-response GH trial evaluated the effect of two dosages of GH, 3 and 6 IU GH/m^2 body surface·d (~0.033 or 0.067 mg/kg·d), on long-term growth and ultimately on AH. Inclusion criteria were 1) birth length SDS below −1.88 (11), 2) CA between 3–11 yr in boys and 3–9 yr in girls at the start of the study, 3) height SDS for CA (height SDS) below −1.88 (12), 4) height velocity (HV) SDS for CA zero or less (12) to exclude children presenting spontaneous catch-up growth, 5) prepubertal stage (defined as Tanner breast stage I for girls and a testicular volume <4 ml for boys) (13), 6) uncomplicated neonatal period [that is, without signs of severe asphyxia (defined as an Apgar score <3 after 5 min), without sepsis neonatorum, and without long-term complications of respiratory ventilation]. Exclusion criteria were endocrine or metabolic disorders, chromosomal disorders, growth failure caused by other disorders (emotional deprivation, severe chronic illness, or chondrodysplasia) or syndromes (except for Silver-Russell syndrome) and previous or present use of drugs that could interfere with GH treatment. Twenty-seven of the 79 patients had partial GH deficiency (GHD), which was defined as a maximal peak GH secretion between 10–20 mU/liter during two GH provocation tests or during one provocation test and a 24-h GH profile (5, 14).

The GH trial started in 1991 and was approved by the ethics committees of the four participating centers in The Netherlands. Due to ethical considerations the ethics committees did not allow for a control group until AH. Written informed consent was obtained from the parents or guardians of each child.

Control group

In 1990, 107 children born in three academic hospitals with a birth length below −1.88 SDS in the same time period as the GH-treated group (1980 until 1989), were included in a cohort study to evaluate natural growth in SGA children with short stature at the age of 2 yr (3). Fifty-nine children were lost due to either start of GH treatment (n = 21), treatment for precocious puberty (n = 1), spastic paraplegia (n = 1), or lack of motivation or moving abroad (n = 36). During the inclusion period of the GH trial, 29 children met the inclusion criteria of our GH trial, including persistent short stature without signs of catch-up growth (HV SDS, <0), but they remained untreated because their pediatrician did not participate in the GH trial. None of these children was GH deficient. This group was followed as a control group for the GH trial. In 2001, 15 children had reached AH and served as controls for comparison of growth and AH of the 54 GH-treated children.

Design dose-response GH trial

After stratification for CA and spontaneous GH secretion during a 24-h GH profile, 79 children were randomly and blindly assigned to one of two GH dosage groups: group A, 3 IU/m^2·d; or group B, 6 IU/m^2·d (~0.033 or 0.067 mg/kg·d, respectively) (5, 6). The inclusion period

started in April 1991 and ended in January 1993. Biosynthetic GH (r-hGH Norditropin, Novo Nordisk A/S, Copenhagen, Denmark) was given sc once daily at bedtime with a pen injection system (Nordiject 24). Every 3 months the total GH dose was adjusted to the calculated body surface. To ensure the double-blind design, an equal volume of a reconstituted preparation was used.

Growth evaluation

During 11 yr one physician (from 1991–1995, W. de Waal; from 1995–1998, T. Sas; from 1998–2002, Y. van Pareren) examined all children every 3 months and measured height according to Cameron using a Harpenden stadiometer (15). Four measurements per visit were taken, and the mean was used for analysis. Height was expressed as the SDS for CA (height SDS) (12). Target height (TH) was adapted from Dutch reference data with the addition of 3 cm for secular trend: $1/2 \times$ (height$_{father}$ + height$_{mother}$ + 12) + 3 for boys and $1/2 \times$ (height$_{father}$ + height$_{mother}$ − 12) + 3 for girls (12). TH and body mass index (BMI) were expressed as the SDS using Dutch references (12). TH range was defined as the mean TH ± 2 SD. Bone age (BA) was determined by the same investigators (1991–1998, T. Sas; 1998–2001, Y. van Pareren) according to the Tanner and Whitehouse radius, ulna, short bones score (RUS TW-2) (16). Bone maturation was expressed as the ratio of the change in BA to the change in CA. The difference between CA and BA was calculated as CA minus BA (CA − BA) in years. The same investigators assessed pubertal stage according to Tanner, using an orchidometer in boys. The start of puberty was defined as a Tanner breast stage II in girls and a testicular volume of 4 ml in boys (13).

Definition of AH

AH in GH-treated children was defined as the condition when HV had dropped less than 0.5 cm during the previous 6 months and bone age was 15 yr or greater for girls and 16.5 yr or greater for boys. AH was reached either during GH treatment or during the 2-yr follow-up after discontinuation of GH treatment. Corrected AH was calculated by subtracting the target height (TH) SDS from the AH SDS. GH treatment was discontinued after reaching AH or on the patient's decision at near AH (near AH), which was defined as a HV ranging between 0.5–2 cm during the previous 6 months. For the control group, AH was defined as the condition when CA and/or BA had reached 18 yr for boys and 16 yr in girls.

Biochemical parameters

Before the start and after discontinuation of GH treatment a standard arginine tolerance test (ATT) was performed (5). A standard oral glucose tolerance test was performed at the start of GH treatment and after 6 yr of GH treatment (17). At the start of GH treatment and during the dose-response GH trial additional blood samples were taken for determination of plasma levels of IGF-I and hemoglobin A$_{1c}$ levels. Plasma levels of IGFBP-3 were determined at the start of GH treatment and after the first and second years and after the fifth year of GH treatment. After centrifugation, all samples were frozen (−20 C) until assayed.

TABLE 1. Baseline clinical data for the total group of 79 short children born SGA and for the 54 children who reached AH

	Total group (n = 79)		AH group (n = 54)	
	Group A (n = 41)	Group B (n = 38)	Group A (n = 28)	Group B (n = 26)
Male/female	31/10	21/17	18/10	14/12
Gestational age (wk)	37.3 (3.2)	36.0 (4.1)	37.1 (3.4)	36.2 (4.3)
Birth length SDS	−3.6 (1.4)	−3.7 (1.4)	−3.5 (1.3)	−3.6 (1.5)
Birth weight SDS	−2.6 (1.2)	−2.6 (1.0)	−2.6 (1.1)	−2.6 (0.8)
CA (yr)	6.6 (2.4)	6.7 (2.9)	7.9 (1.9)[a]	8.2 (1.9)[a]
Height SDS	−3.0 (0.7)	−3.1 (0.7)	−2.9 (0.8)	−3.0 (0.7)
HV SDS	−0.7 (1.1)	−1.2 (1.3)	−0.6 (1.1)	−1.4 (1.4)

Data are expressed as the mean (±SD).
[a] $P < 0.001$, mean (±SD) CA of 54 children with AH [8.1 (1.9)] *vs.* 19 who were still growing [5.4 (1.9)].

Hormone assays

RIA measurements of plasma GH, IGF-I, IGFBP-3, and insulin were performed as described previously (18–21). All measurements were performed in the same laboratories. As plasma levels of both IGF-I and IGFBP-3 are dependent on age and sex, values were transformed to SDSs using reference values for healthy children determined in the same laboratory (22).

Statistical analyses

To maintain the double-blind design until all participants reached AH, an independent statistician (P.M.) performed the statistical analyses and summarized the results per treatment group in such a way that it was impossible for the investigator to identify individual patients. Accordingly, data are expressed as mean (±SD) values unless otherwise specified. Differences in continuous variables were tested by paired *t* tests. Differences between zero and SDS values at various time points during the study were tested by one-sample *t* tests. Differences between groups were tested using a two-sample *t* test. To test for relationships between continuous variables, correlations were estimated after adjustment for GH dosage. Multiple linear regression analyses were used to construct the best model for predicting AH SDS. For this purpose, the variables GH dose, TH SDS, height SDS at the start of GH treatment, CA − BA at the start of GH treatment, birth length SDS, gender, CA at the start of the study, bone maturation during the first year, age at onset of puberty, and BMI SDS at the start were tested. $P < 0.05$ was considered significant. All calculations were executed in SPSS version 9.0 (SPSS, Inc., Chicago, IL).

Results

GH trial

Fifty-four children reached AH after a mean (±SD) GH treatment period of 7.9 (1.7) yr for group A and 7.5 (1.7) yr for group B. Pretreatment clinical data are listed in Table 1 for the total group and for the 54 children who reached AH. Both groups had similar clinical characteristics at the start of GH treatment, except for age.

AH

GH treatment resulted in a mean (±SD) AH SDS of −1.1 (0.7) for group A (3 IU/m²·d) and −0.9 (0.8) for group B (6 IU/m²·d; Table 2). In both groups, the AH SDS was significantly higher than the height SDS at the start of GH treatment ($P < 0.0001$). The difference in AH SDS between groups A and B did not reach significance [mean difference, 0.3 SDS; 95% confidence interval (CI), −0.2, 0.6; $P = 0.3$]. Figure 1 gives the height SDS at the start of the study, after 2 and 5 yr of GH treatment, and at AH and the gain in height SDS from the start until AH. The mean (±SD) gain in height SDS from the start until AH was not significantly different for group A [from −2.9 (0.8) at start to −1.1 (0.7)] compared with group B [from −3.0 (0.7) to −0.9 (0.8); mean difference, 0.3 SDS; 95% CI, −0.1, 0.7; $P = 0.1$]. Table 2 lists the height SDS throughout the study, TH SDS, AH SDS, and the corrected AH SDS (AH SDS minus TH SDS). The mean (±SD) TH SDS was almost significantly lower for group A [−0.9 (1.0)] than for group B [−0.5 (0.9); mean difference, 0.5; 95% CI, 0.1, 1.0; $P = 0.08$]. As a result the mean (±SD) corrected AH SDS was not significantly different between group A [−0.2 (0.8)] and group B [−0.4 (0.9); mean difference, 0.2; 95% CI, −0.2, 0.7; $P = 0.2$]. Figure 2 shows the corrected height SDS at the various time points of the study. At the start and after 2 yr of GH treatment, the corrected height SDS was significantly less than zero for groups A and B ($P < 0.001$ and $P < 0.001$, respectively). At AH, the corrected height SDS was comparable to zero for group A, but was lower for group B ($P < 0.05$). For boys, both TH SDS and AH SDS were significantly higher for group B than for group A ($P < 0.01$, $P < 0.05$, and $P < 0.05$, respectively; Table 2). For girls, however, no difference was found for TH SDS and AH SDS between groups A and B ($P > 0.1$).

TABLE 2. AH SDS and other auxological data in 54 SGA children at various time points during the study

	All children SGA		Non-GH-deficient SGA		Partially GH-deficient SGA	
	Group A (n = 28)	Group B (n = 26)	Group A (n = 17)	Group B (n = 20)	Group A (n = 11)	Group B (n = 8)
Duration of GH treatment (yr)	7.9 (1.7)	7.5 (1.7)	8.1 (1.9)	7.6 (1.8)	7.7 (1.5)	7.2 (1.2)
Height SDS						
At start	−2.9 (0.8)	−3.0 (0.7)	−2.9 (0.7)	−3.0 (0.8)	−3.0 (0.8)	−3.1 (0.3)
2 yr	−1.5 (0.7)	−1.3 (0.7)	−1.5 (0.7)	−1.3 (0.8)	−1.5 (0.7)	−1.3 (0.3)
5 yr	−0.7 (0.7)	−0.7 (0.8)	−0.7 (0.7)	−0.6 (0.8)	−0.8 (0.6)	−0.9 (0.7)
AH	−1.1 (0.8)	−0.9 (0.8)	−1.1 (0.8)	−0.9 (0.8)	−1.2 (0.7)	−0.8 (0.7)
Corrected height SDS (height SDS − TH SDS)						
At start	−2.0 (0.9)	−2.6 (0.6)[a]	−2.2 (0.9)	−2.7 (0.9)	−1.9 (0.9)	−2.2 (0.4)
2 yr	−0.6 (0.9)	−0.0 (0.8)	−0.7 (1.0)	−1.0 (0.9)	−0.4 (0.9)	−0.3 (0.4)
5 yr	0.2 (0.8)	−0.2 (1.0)	0.1 (0.9)	−0.3 (1.1)	0.4 (0.8)	0.0 (0.4)
AH	−0.2 (0.8)	−0.4 (0.9)	−0.3 (0.8)	−0.8 (1.0)	−0.1 (0.7)	0.0 (0.2)[b]
TH SDS	−0.9 (1.0)	−0.5 (0.9)	−0.8 (1.0)	−0.3 (0.9)	−1.1 (0.9)	−0.9 (0.6)
Adult height (cm)						
Boys	169.3 (6.7)	173.7 (5.8)				
Girls	160.1 (3.1)	159.2 (4.0)				
Pubertal height gain (cm)						
Boys	27.3 (7.6)	30.0 (5.3)				
Girls	18.8 (6.9)	19.4 (5.8)				

Data are expressed as the mean (±SD). Data on AH (centimeters) and pubertal height gain (centimeters) for non-GHD *vs.* GHD are not shown due to the small number of children in each subgroup.
[a] $P < 0.05$, group A *vs.* group B.
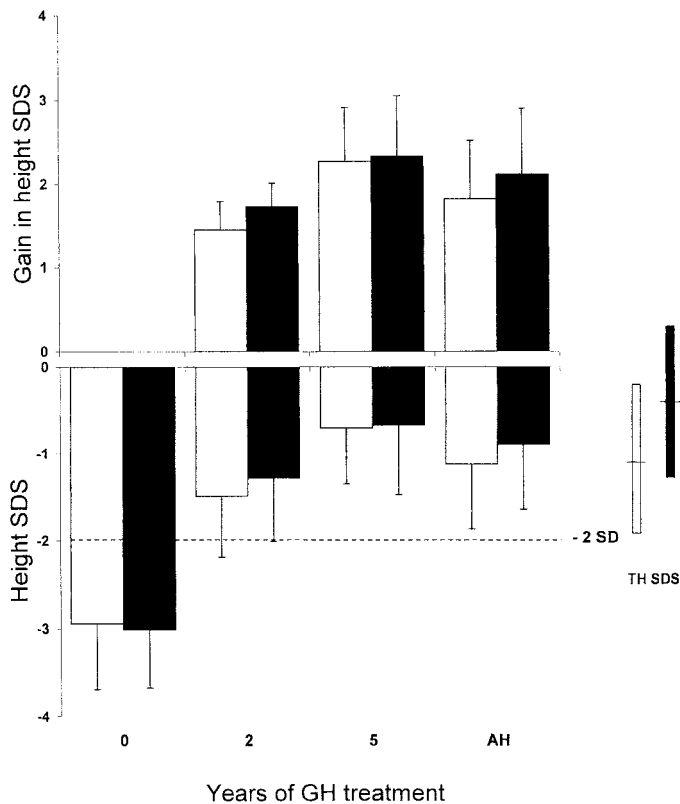[b] $P < 0.05$, non-GHD *vs.* partially GHD children.

tween the non-GHD and the partially GHD SGA children, even when corrected for GH dose and TH SDS.

Puberty

The mean ($\pm$SD) age at onset of puberty for boys was 11.7 (0.9) yr in group A and 11.8 (0.7) yr in group B, and that for girls was 10.9 (1.1) yr in group A and 10.8 (1.1) yr in group B, without a significant difference between the GH dosage groups ($P > 0.1$ for both sexes). For boys, the mean age ($\pm$SD) at AH was 16.8 ($\pm$0.9) yr in group A *vs.* 16.9 (1.1) yr in group B, and for girls, it was 14.8 (0.8) *vs.* 15.1 (1.2) yr in groups A and B, respectively. The age at AH was not different between the GH dosage groups ($P > 0.1$ for both sexes). The mean duration of puberty (from the start of puberty until AH) for boys was 5.1 (1.2) yr in group A and 5.2 (1.0) yr in group B, and that for girls was 3.9 (1.0) yr in group A and 4.3 (1.1) yr in group B.

Bone maturation

The average bone maturation, expressed as change in (Δ)BA/ΔCA per year, was throughout the study significantly higher than 1 regardless of GH dosage. During the first year of GH treatment, the median (range) bone maturation was 1.5 (0.6–2.7) yr for group A and 1.1 (0.2–3.2) yr for group B. From 4–5 yr of GH treatment, bone maturation was 1.1 (0.3–2.5) yr for group A and 1.0 (0.3–2.2) yr for group B, and from 5 yr until discontinuation of GH treatment, bone maturation was 1.0 (0.3–1.6) yr for group A and 1.1 (0.4–1.7) yr for group B. The average differences between CA and BA (CA − BA) at the start of GH treatment, at 5 yr of GH treatment, and at discontinuation of GH treatment were 0.5 (1.1), −1.0 (1.1), and −1.1 (1.1), respectively, without significant differences between groups A and B.

GH, IGF-I, and IGFBP-3

The non-GHD SGA children who attained AH had at the start of GH treatment a mean ($\pm$SD) maximal GH peak during a GH provocation test of 28.7 (11.5) mU/liter, a mean ($\pm$SD) GH peak during the 24-h GH profile of 37.2 (16.1) mU/liter, and a mean IGF-I SDS of −0.5 (0.8). Seventeen of the 54 SGA children who attained AH had a maximal GH peak between 10–20 mU/liter. In these partially GHD SGA children, the mean ($\pm$SD) maximal GH peak during the GH provocation test, the GH peak during the 24-h GH profile, and the mean IGF-I SDS at the start of treatment were 13.0 (5.8) mU/liter, 20.9 (8.5) mU/liter, and −1.8 (1.2), respectively; all were significantly lower than in the non-GHD SGA children ($P < 0.001$, $P < 0.01$, and $P < 0.001$, respectively).

The changes in IGF-I SDS and IGFBP-3 SDS of the total group during 5 yr of GH treatment were described previously (6). At discontinuation of GH treatment, the mean IGF-I SDS was 1.0 (1.1) for group A and 1.3 (1.2) for group B, being significantly different from zero for both groups ($P < 0.001$ for both). The mean IGFBP-3 SDS at discontinuation of GH treatment was −0.8 (0.9) for group A and −0.06 (0.7) for group B, being significantly lower than zero for group A only ($P < 0.001$). Only for IGFBP-3 SDS was the difference between groups A and B at discontinuation of GH treatment significant ($P < 0.01$).

FIG. 1. *Bottom panel*, Height SDS ($\pm$SD) during GH treatment and at AH in relation to TH. *Top panel*, Gain in height SDS ($\pm$SD) from the start until 2 yr of GH treatment, until 5 yr of GH treatment, and until AH. □, Group A; ■, group B.

FIG. 2. Corrected height SDS ($\pm$SD) during GH treatment and at AH for group A (□) and group B (■).

AH of non-GHD vs. partially GHD SGA children

The AH SDS of the non-GHD children was −1.1 (0.8) for group A and −0.9 (0.8) for group B compared with −1.2 (0.7) for group A and −0.9 (0.7) for group B in the partially GHD children (Table 2). The mean height gain SDS of the non-GHD children was 1.9 (0.8) for group A and 2.1 (0.8) for group B, compared with 1.8 (0.5) for group A and 2.2 (0.6) for group B in the partially GHD children. The AH SDS as well as the height gain SDS were not significantly different be-

Predictors of AH

All correlations were made for groups A and B together, after adjustment for GH dose, although no significant differences in AH SDS and gain in height SDS were found between groups A and B. The AH SDS correlated positively with height SDS at the start of GH treatment (r = 0.49; $P <$ 0.001), TH SDS (r = 0.49; $P <$ 0.001), and pretreatment HV SDS (r = 0.32; $P <$ 0.05). The AH SDS was not significantly related to the following variables: CA and BA at the start of GH treatment, birth length SDS, maximal GH peak during ATT, characteristics of the 24-h GH profiles, IGF-I SDS values at the start of GH treatment, and increment in IGF-I SDS during the first year of GH treatment.

The gain in height SDS from the start of GH treatment until AH had a negative correlation with CA and BA at the start of GH treatment (r = −0.36; $P <$ 0.01 and r = −0.46; $P <$ 0.01, respectively). Birth length SDS, TH SDS, pretreatment HV SDS, IGF-I SDS at the start of GH treatment, increase in IGF-I SDS, mean maximal plasma GH response during ATT, and characteristics of the 24-h GH profiles did not correlate significantly with the gain in height SDS from the start of GH treatment until AH.

Multiple regression analysis showed that a model, using the variables TH SDS, height SDS at the start of GH treatment, CA − BA at the start of GH treatment, and the GH dose accounted for 42% (residual SD, 0.60) of the variation in AH SDS. Table 3 shows the results of the multiple regression analysis. Variables that showed a nonsignificant effect on AH SDS were gender, CA at start of treatment, bone maturation during the first year, age at onset of puberty, BMI SDS at start of treatment, birth length SDS, and GH dose. The model provided the following equation: AH SDS = 0.02 + 0.29 × TH SDS + 0.42 × height SDS at start + 0.20 × (CA − BA in years) at start + 0.07 × GH dose.

Safety

Treatment was well tolerated, and no adverse events were detected that were considered to be GH related. Our group has recently published 6-yr results on fasting and stimulated glucose and insulin levels during an oral glucose tolerance test (17). In short, continuous GH treatment over a 6-yr period had no adverse effect on glucose levels. GH treatment induced higher fasting insulin levels and glucose-stimulated insulin levels, indicating relative insulin resistance. No significant differences between the two GH dosage groups were found. None of the children developed diabetes mellitus.

Control group

The control group, 15 children (5 boys and 10 girls), had a mean (±SD) birth length SDS of −3.3 (1.2), a birth weight

TABLE 3. Multiple regression analysis on AH SDS

Independent variable	Regression coefficient	SE	P value
TH SDS	0.29	0.10	<0.01
Height SDS at start	0.43	0.14	<0.01
Difference CA-BA at start (yr)	0.20	0.08	<0.05
GH dose (3 *vs.* 6 IU/m²/day)	0.07	0.06	0.2

Regression equation: AH SDS = 0.02 + 0.29 × TH SDS + 0.43 × height SDS at start + 0.20 × (CA-BA) at start + 0.07 × GH dose.

SDS of −2.7 (0.7), and a mean (SD) gestational age of 34.3 (2.3) wk. At inclusion in the control group, the mean (±SD) age was 7.8 (1.7) yr, height SDS was −2.6 (0.5), TH SDS was −1.1 (1.0), and corrected height SDS was −1.5 (0.9). No significant difference was found between the GH-treated group and the control group in pretreatment clinical characteristics, except for gestational age ($P <$ 0.05).

AH of GH-treated vs. control group

The control group attained a mean (±SD) AH SDS of −2.3 (0.7) after a mean (±SD) follow-up of 7.5 (1.2) yr from inclusion in the control group until AH. The mean (±SD) gain in height SDS until AH was 0.3 (0.7) SDS, and the corrected AH was −1.2 (0.6) SDS. The mean AH SDS, gain in height SDS until AH, and corrected AH SDS were all significantly lower than those in the GH-treated group [mean differences (95% CI), 1.3 (0.9, 1.8), 1.7 (1.3, 2.3), and 0.9 (0.4, 1.4), respectively; $P <$ 0.001 for all].

Discussion

Our study shows that in short children born SGA, long-term continuous treatment with GH results in a normalization of height during childhood and a normalization of AH in most children. After a mean duration of 7.8 yr, children treated with 3 IU GH/m²·d (group A) attained a mean (±SD) AH SDS of −1.1 (0.7), whereas those treated with 6 IU GH/ m²·d (group B) attained a mean AH SDS of −0.9 (0.8). GH treatment resulted in an AH within the normal range (above −2.0 SDS) in 85% of the children and an AH within the TH range in 98%. Interestingly, AH SDS was not significantly different between the two GH dosage groups. Also, the mean gain in height SDS from the start of treatment until AH [1.8 (0.7) SDS (an improvement of ~12 cm for boys and ~11 cm for girls) for group A and 2.1 (0.8) SDS (an improvement of ~14 cm for boys and ~13 cm for girls) for group B] was not significantly different between the two GH dosage groups.

When we corrected AH SDS for TH SDS, because group A had a significantly lower TH SDS than group B, the mean corrected AH SDS (AH SDS minus TH SDS) proved to be comparable for group A [−0.2 (0.8)] and group B [−0.4 (0.9)]. This means that when AH SDS was corrected for the genetic potential (TH), children who had been treated with the lower GH dose of 3 IU/m²·d had the same results. Our study shows that 98% of short children born SGA treated with long-term GH reached an AH within their TH range.

Two nonrandomized studies reported on AH in a group of short children born SGA with GHD (23, 24). They found a mean height SDS gain from start of the study until AH of 0.5 and 0.9 SDS, which is much lower than we now report. There are, however, several factors that can explain the discrepancy between their results and ours. Their children were older (10.9 and 10.7 yr) at the start and were treated for a much shorter period than our children (4.6 yr for both studies). In addition, in the study by Coutant *et al.* (23) children were treated with a wide range of GH dosages and with a low mean GH dose of 1.8 IU/m²·d (almost half of our lowest GH dose).

Because including a randomized control group as part of our GH trial until AH was not allowed by the medical ethics

committees, we compared our GH-treated patients with a longitudinally followed control group with the same inclusion criteria and age as the GH-treated patients at the start of treatment who did not receive GH treatment because the pediatrician did not participate in the GH trial. The control group attained a mean ($\pm$SD) AH SDS of -2.3 (0.7), had a mean gain in height SDS of 0.3 (0.7) until AH during the follow-up period of 7.5 yr, and had a corrected AH of -1.2 (0.6) SDS. These data show that compared with untreated short children born SGA, those treated with GH significantly gained in AH SDS. The proportion of girls in the control group, however, was larger than that in the GH groups. It is unlikely that this will affect the results, as we show that AH, expressed as SDS, did not differ between genders.

Our study demonstrates that most children reached a normal height after the first years of GH treatment and remained in the normal range until AH. This means that most of them had a normal height during childhood and puberty. At the end of GH treatment, a slight decrease in height SDS was found in comparison with height SDS after 5 yr of GH treatment. Possible explanations for this decline might be an early onset of puberty, a short duration of puberty, and/or an acceleration of bone maturation. This would lead to attainment of AH at a relatively young age compared with peers and/or a reduced pubertal height gain. We found, however, that for both GH dosage groups, the mean age at onset of puberty was comparable to that in normal Dutch children (median age for healthy boys is 11.5 yr and for girls is 10.7 yr), whereas from the onset of puberty until AH the mean pubertal height gain was 29.8 cm for boys and 18.9 cm for girls (25). In accordance, during puberty, no acceleration of bone maturation was found until discontinuation. Previous publications have shown, however, that untreated children born SGA start their pubertal growth spurt earlier than normal children (26, 27). We found that the difference between CA and BA (CA $-$ BA) after 5 yr of GH treatment was -1.0, indicating a 1-yr bone age advance. This might explain the slight decrease in height SDS. As we found no significant difference between the two GH dosage groups, it is unlikely that the 1-yr bone age advance was related to the GH treatment. Another factor that might explain the decrease in height SDS is that some of the children did not reach their full height potential because they stopped GH treatment at near-AH.

AH SDS, when corrected for GH dosage, was higher in children with the highest TH SDS and height SDS at start of GH treatment. Although age at the start of treatment was weekly correlated with height gain from the start of treatment until AH, it was not associated with AH SDS. Why other studies did find an association might be explained by the fact that they started treatment at a later mean CA, which implied a shorter duration of GH treatment (4.6 yr) until AH than in our group (23). Over the long-term, other factors that influence AH (*i.e.* genetic background) might become more important. In our opinion, however, this should not lead to postponing GH treatment until puberty. Not only would the treatment period then be too short, but the important advantages of a normal height during childhood and adolescence would be lost.

The GHD children included in our study were not severely GHD, but only partially GHD. Their growth and AH results were similar to those without GHD. Also, in the total study group no correlation was found between spontaneous or stimulated GH secretion before the start of GH treatment and AH SDS or gain in height SDS. Our findings agree with other reports showing no association between response to GH treatment and GH status before start (28, 29). This indicates that GH treatment is effective in short children born SGA, leading to a normal AH for most of them regardless of the GH status at start.

The recommended GH dose will depend on the ultimate goal in short children born SGA. First, one might aim for a normal AH, meaning an AH above -2 SDS. Secondly, one could set out for an AH within the TH range SDS. To visualize the effects of each of these goals on the decision of which GH dose to use, we constructed a prediction model (Table 3). The prediction model for AH SDS shows that several variables influence AH SDS: TH SDS, height SDS at the start of treatment, and CA $-$ BA at the start of treatment. For all of these variables a higher value predicts an increment in AH SDS. These variables are not surprising, as they have also been found to predict height gain and AH in other patient groups, but they indicate that similar factors play a role in response to GH treatment in short SGA children (30, 31). Suppose a child born SGA starts GH treatment when he or she has a persistent short height of -2 SDS and no BA delay (CA $-$ BA = 0; Table 4). Our model then predicts that when this child has an average TH SDS (TH SDS = 0) it would achieve an AH of -0.6 SDS after a dose of 3 IU GH/m^2·d [95% prediction interval (PI) between -1.8 and 0.6 SDS]. For a child with a TH SDS of -2 treated with the same GH dose, the predicted AH would be -1.2 SDS (95% PI between -2.4 and 0). When one chooses the first goal, an AH above -2 SDS, both children can be given 3 IU GH/m^2·d. When one decides on the second goal, an AH near the TH SDS, a higher GH dose of 6 IU GH/m^2·d might be considered for a child with a higher TH SDS. Our model, however, shows that by giving the child with a TH of 0 SDS the higher dose, the predicted AH SDS would only increase by 0.2 SDS (-0.4 SDS with 95% PI between -1.6 and 0.8), while doubling the costs of treatment. Another possible reason for considering a higher GH dose could be when the child is very short at the start of GH treatment. The model shows that, using the same values as before (no BA delay and TH SDS = 0), a child with a height SDS at the start of GH treatment of -3 would reach an AH SDS of -1.0 (95% PI between -2.2 and 0.2) when using the low dose and -0.8 SDS (95% PI between -2.0 and 0.4) when using the high dose of GH. As before, the difference in AH would be quite small while doubling the costs of treatment. Obviously, one should keep in mind that the model only

TABLE 4. Examples of predicted AH SDS resulting from the regression model

GH dose (IU/m^2·d):	TH SDS = 0		TH SDS = -1		TH SDS = -2	
	3	6	3	6	3	6
Height SDS at start						
-2	-0.6	-0.4	-0.9	-0.7	-1.2	-1
-3	-1	-0.8	-1.3	-1.1	-1.6	-1.4
-4	-1.5	-1.3	-1.8	-1.5	-2	-1.8

predicts 42% of the difference in AH, leaving 58% of the variation to be explained by other factors, such as genetic background (8, 9). For that reason, larger numbers of GH-treated short SGA children with detailed phenotypic and genetic data are required to allow for a prediction model with a higher predictive value.

In conclusion, long-term, continuous GH treatment in short children born SGA leads to a normalization of height in childhood and adolescence. Eighty-five percent will reach a normal AH, whereas 98% will reach an AH within their TH range. Based on our study we recommend considering GH treatment for short SGA children without signs of persistent catch-up growth and who are therefore at risk of significant height disability as adults. Interestingly, a dose of 3 IU/m$^2 \cdot$d proved to be as effective as the higher GH dose of 6 IU/m$^2 \cdot$d for most children. Only children with extreme short stature or/and a TH below the normal range may need a higher GH dose to normalize height during childhood and in adulthood. Further studies should aim at optimizing GH treatment by developing advanced prediction models indicating the best treatment options for each child.

Acknowledgments

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