Final Height in Girls with Turner Syndrome after Long-Term Growth Hormone Treatment in Three Dosages and Low Dose Estrogens

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Although GH treatment for short stature in Turner syndrome is an accepted treatment in many countries, which GH dosage to use and which age to start puberty induction are issues of debate. This study shows final height (FH) in 60 girls with Turner syndrome treated in a randomized dose-response trial, combining GH treatment with low dose estrogens at a relatively young age.

Girls were randomly assigned to group A (4 IU/m²·d; ~0.045 mg/kg/d), group B (first year, 4 IU/m²·d; thereafter 6 IU/m²·d), or group C (first year, 4 IU/m²·d; second year, 6 IU/m²·d; thereafter, 8 IU/m²·d). After a minimum of 4 yr of GH treatment, at a mean age of 12.7 ± 0.7 yr, low dose micronized 17β-estradiol was given orally. After a mean duration of GH treatment of 8.6 ± 1.9 yr, FH was reached at a mean age of 15.8 ± 0.9 yr. FH, expressed in centimeters or SD score, was 157.6 ± 6.5 or −1.6 ± 1.0 in group A, 162.9 ± 6.1 or −0.7 ± 1.0 in group B, and 163.6 ± 6.0 or −0.6 ± 1.0 in group C. The difference in FH in centimeters, corrected for height SD score and age at start of treat-ment, was significant between groups A and B [regression coefficient, 4.1; 95% confidence interval (CI), 1.4, 6.9; P < 0.01], and groups A and C (coefficient, 5.0; 95% CI, 2.3, 7.7; P < 0.001), but not between groups B and C (coefficient, 0.9; 95% CI, −1.8, 3.6). Fifty of the 60 girls (83%) had reached a normal FH (FH SD score, more than −2). After starting estrogen treatment, the decrease in height velocity (HV) changed significantly to a stable HV, without affecting bone maturation (change in bone age/change in chronological age). The following variables con-tributed significantly to predicting FH SD score: GH dose, height SD score (ref. normal girls), chronological age at start of treatment, and HV in the first year of GH treatment. GH treatment was well tolerated.

In conclusion, GH treatment leads to a normalization of FH in most girls, even when puberty is induced at a normal pu-bertal age. The optimal GH dosage depends on height and age at the start of treatment and first year HV. (*J Clin Endocrinol Metab* 88: 1119–1125, 2003)

T HE MOST COMMON clinical characteristic of Turner syndrome (TS) is short stature. The reason for the short stat-ure is still under investigation. A recent study has shown that the etiology of the growth retardation possibly lies in the hap-loinsufficiency of the SHOX gene (1). Although girls with TS are not GH deficient (2), subnormal levels of GH and IGF-I have been reported (3, 4). It has been postulated that a diminished sensitivity for growth factors might explain their growth retar-dation (5, 6). Nevertheless, GH treatment in a supraphysiologi-cal dosage has been shown to accelerate growth (4, 7). Another clinical feature in most girls with TS is the absence of sponta-neous pubertal development, for which estrogen substitution is necessary. Although GH treatment for short stature in TS is now an accepted treatment in many countries, reports on final height are inconsistent (8, 9), and which dosage to use and which age to start puberty induction are issues of debate.

Previously, we have demonstrated that long-term GH treat-ment in TS leads to normalization of height (4, 10). This study shows final height (FH) results in 60 girls with TS treated in a randomized dose-response trial comparing 3 dosage schedules. In addition, we show the effect of low dose estrogen treatment begun at a relatively young age. Thereby, we have constructed a prediction model for FH SD score to aid individual treatment.

Subjects and Methods

Study subjects

Sixty-eight previously untreated girls with TS were enrolled from 8 academic and 3 major nonacademic pediatric departments in The Neth-

erlands in an open randomized multicenter GH dose-response study. Six girls dropped out of the study because of noncompliance and were lost to follow-up. Two girls were still being treated with GH at the time of analysis (January 24, 2002) and had not yet reached FH, leaving 60 girls for analysis of FH in this study (Fig. 1). As the 8 girls not used in the analysis (either lost to follow-up or had not yet reached FH) were normally distributed over the randomization groups (4/3/1), and the baseline clinical data showed no significant difference compared with the 60 girls with FH, selection bias was unlikely.

The diagnosis was confirmed by lymphocyte chromosomal analysis. Three of the 68 girls had a prenatal diagnosis. Inclusion criteria were chronological age (CA) between 2–11 yr, height below the 50th percentile for healthy Dutch girls (11), and normal thyroid function. Exclusion criteria were associated endocrine and/or metabolic disorders, growth failure caused by other disorders or emotional deprivation, hydrocephalus, previous use of drugs that could interfere with GH treatment, and spontaneous puberty (12). Written informed consent was obtained from the girls and their parents or guardians. The study protocol was approved by the ethics committee of each participating center.

Study design

At start of the study a total of 15 patients/dosage group was calculated to be necessary to discover a true mean difference in height velocity (HV) of 1.0 cm/yr between dosage groups after 2 treatment yr with a probability of 80% (based on a two-sided *t* test for paired observations). Based on this calculation, 68 girls were included from November 1989 until October 1990 in the study to evaluate the effect of augmentation of GH dosage on HV and FH. Sixty-eight girls were randomly assigned to 3 groups in blocks of 2, 4, or 6 (randomly chosen) in 4 strata defined by age and height SD score at the start of treatment. The sequence was concealed in envelopes until treatment was assigned. The treatment regiments were: group A (n = 23), 4 IU/m² body surface·d (~0.045 mg/kg·d); group B (n = 23), 4 IU/m²·d in the first year, followed by 6 IU/m²·d (~0.0675 mg/kg·d); and group C (n = 22), 4 IU/m²·d in the first year, 6 IU/m²·d in the second year, and thereafter 8 IU/m²·d (~0.090 mg/kg·d).

Biosynthetic human GH (Norditropin, Novo Nordisk A/S, Bagsvaerd, Denmark) was given sc once daily at bedtime using a pen injection system. Every 3 months the total GH dose was adjusted to the

calculated body surface. According to the study protocol, the GH treatment was discontinued when HV was less than 1 cm over 6 months or on the decision of the patient due to satisfaction with achieved height. In the first 4 yr of GH treatment, no estrogen for pubertal induction was given to the girls. After 4 yr of GH treatment, estrogen treatment was started at the yearly visit after the subject had reached the age of 12 yr. In the girls who became 12 yr old during the first 4 yr of GH treatment, estrogen treatment was started at 4 yr of GH treatment. Five micrograms of 17β-estradiol/kg body weight·d (~0.05 μg ethinyl estradiol/kg·d), orally, were given in the first 2 yr, 7.5 μg/kg·d in the third year, and 10 μg/kg·d thereafter (tablets containing 0.1 mg micronized 17β-estradiol were supplied for the study by Novo Nordisk A/S). Cyclic progesterone therapy (Duphaston, Solvay Pharmaceuticals BV, Weesp, The Netherlands; 5 mg/d during the first 14 d of the month) was added after 2 yr of estrogen therapy. If puberty had developed spontaneously (Tanner breast stage ≥2) before the start of estrogen treatment, no exogenous estrogen was given.

Height was measured in eight academic and three major nonacademic pediatric departments at baseline and subsequently every 3 months in the same department using a Harpenden stadiometer by three observers (A.v.T., 1989–1995; T.S., 1995–1998; Y.v.P., 1998–2001). The mean of four measurements was used for analysis. FH was defined as the most recent available height after discontinuation of GH treatment (mean ± SD, 0.5 ± 0.2 yr after discontinuation of GH treatment). Height was expressed as the SD score using the references for healthy normal Dutch girls (ref. normal girls) (13) or the references for North European untreated girls with TS (ref. TS) (14). HV per year was defined as the increase in height in centimeters per year. The HV SD score was calculated using reference values for HV in North European untreated girls with TS (15). Target height (TH) was adapted from Dutch reference data with addition of 4.5 cm for secular trend: TH = 1/2 × (H_{mother} + H_{father} − 13 cm) + 4.5 cm (13). TH range was defined as the TH ± 1.3 SD, and TH was expressed as the SD score (13, 16). During GH treatment pubertal stages were assessed according to Tanner (12). Bone age (BA) was determined by the same three observers according to the Tanner and Whitehouse radius, ulna, short bones score (17). Bone maturation was expressed as the ratio of the change in BA to the change in CA (ΔBA/ΔCA). Adult height without GH treatment was calculated for each girl with the modified projected adult height method (mPAH), using the equation of Lyon, adapted to North European untreated girls with TS (14, 18, 19). To assess the gain in FH, FH was compared with the mPAH at the start of GH treatment.

Biochemical parameters and hormone assays

Blood samples were taken at the start of the study, subsequently every year, and 6 months after the discontinuation of GH treatment for determination of the glycosylated hemoglobin, leukocytes, hemoglobin, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, free T_4, and TSH levels. Plasma IGF-I levels were determined at the start of treatment; at 6, 18, 30, and 48 months of treatment; thereafter every year visit until discontinuation of GH treatment; and 6 months after discontinuation of GH treatment. After centrifugation, all samples were frozen (−20 C) until assayed. All measurements of IGF-I were performed in one laboratory by RIA as described previously (20) and were transformed to SD scores using reference levels for healthy children determined in the same laboratory (21).

Statistical analysis

Results are expressed as the mean ± SD unless indicated otherwise. Differences between the dosage groups were tested by linear regression analysis with the variables age and height SD score (ref. normal girls) at the start of treatment and two dummy variables for dosage group. Differences in time between continuous variables were compared by paired two-sided *t* test for the whole group unless otherwise specified. A stepwise forward linear regression analysis was used to construct a prediction model for FH SD score and gain in height (FH − mPAH in centimeters). The following potential predictor variables were used: BA, CA, height SD score (ref. normal girls), and IGF-I SD score at the start of treatment; GH dosage group; target height SD score; karyotype (45,X or other); first year increase in alkaline phosphatase and in HV (in centi-
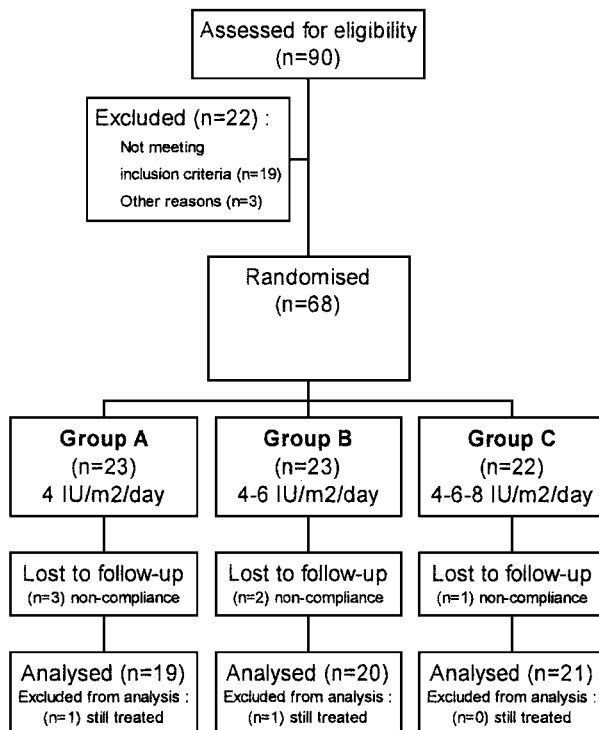

FIG. 1. Flow diagram of the progress through the phases of the trial.

meters); and first 18 months increase in IGF-I SD score. Only the variables with a $P < 0.05$ were kept in the model. Subsequently, the squares of the remaining variables were tested for significance, after which the variables were tested for possible interactions. All correlations were partial correlations, adjusted for GH dosage. $P < 0.05$ was considered significant. All calculations were performed using SPSS version 9.0 (SPSS, Inc., Chicago, IL).

Results

In Table 1 the pretreatment clinical data of the 60 girls with FH are shown. Baseline clinical data were similar for the three GH dosage groups. After a mean duration of GH treatment of 8.6 ± 1.9 yr, FH was reached at a mean age of 15.8 ± 0.9 yr, and with a bone age of 15.5 ± 0.6 yr. Forty-eight of the 60 girls had GH treatment duration of 7 yr or more.

FH was 157.6 ± 6.5 cm in group A, 162.9 ± 6.1 cm in group B, and 163.6 ± 6.0 cm in group C (Table 2). When translated to SD score, using references for normal girls, FH was -1.6 ± 1.0 cm for group A, -0.7 ± 1.0 cm for group B, and -0.6 ± 1.0 cm for group C (Fig. 2). The difference in FH (centimeters), corrected for height SD score and age at the start of treatment, was significant between groups A and B [regression coefficient, 4.1; 95% confidence interval (CI), 1.4, 6.9; $P < 0.01$] and between groups A and C (coefficient 5.0; 95% CI, 2.3, 7.7; $P < 0.001$), but not between groups B and C (coefficient, 0.9; 95% CI, -1.8, 3.6). Fifty of the 60 girls (83%) had reached a normal FH (FH SD score, more than -2). Thirty-eight of the 60 girls (63%) reached an FH within their TH range.

The mean gain in final height (FH $-$ mPAH) in group A was 11.9 ± 3.6 cm, being significantly lower compared with 15.7 ± 3.5 cm in group B (regression coefficient, 4.2; 95% CI, 1.5, 6.9; $P < 0.01$) and compared with 16.9 ± 5.2 cm in group

C (coefficient, 5.2; 95% CI, 2.6, 7.8; $P < 0.001$), but the height gain in group B was not significantly different from that in group C (coefficient, 1.0; 95% CI, -1.6, 3.6; $P = 0.44$; Fig. 3). Similarly, the mean increase in SD score from start of GH treatment until FH in groups B and C was significantly higher compared with that in group A (coefficient, 0.7; 95% CI: 0.31, 1.11; $P < 0.001$), but the increase in group B was comparable to group C (coefficient, 0.12; 95% CI, -0.27, 0.5; $P = 0.5$; Table 2).

Estrogen effect

Estrogen treatment was started at a mean age of 12.7 ± 0.7 yr. Tanner breast stage 2 was reached at a mean age of 12.9 ± 0.6 yr, and stage 4 at a mean age of 14.8 ± 1.1 yr. HV before and after initiation of estrogen treatment is depicted in Fig. 4A. To homogenize the group for age, only the girls who started estrogen treatment at age 12 yr were analyzed (n = 47). HV in the year after initiation of estrogen treatment compared with the HV in the previous year showed no significant difference ($HV_{0\,yr}$ *vs.* $HV_{1\,yr}$). The downward trend in HV before initiation of estrogen treatment, however, changed significantly to a stabile HV after initiation ($\Delta HV_{-1\,yr-0\,yr}$ *vs.* $\Delta HV_{0-1\,yr}$; $P < 0.05$). Bone maturation ($\Delta BA/\Delta CA$) in the year before and in the year after initiation of estrogen treatment was not significantly different (t = 0 *vs.* t = 1 yr; Fig. 4B). GH dosage, GH duration before start of estrogen, and height at puberty had no significant effect on the differences (between before and after initiation of estrogen) in HV, in the change in HV, or in bone maturation.

TABLE 1. Mean (SD) baseline clinical data

	Group A	Group B	Group C
No. of girls	19	20	21
Chronological age (yr)	6.5 (1.9)	6.9 (2.3)	6.5 (2.4)
Bone age (yr)	5.9 (2.1)	6.2 (2.5)	5.8 (2.4)
Height SD score			
Reference, normal Dutch girls	-2.9 (0.9)	-2.7 (0.9)	-2.7 (1.0)
Reference, Turner	0.0 (1.1)	0.3 (0.9)	0.2 (1.1)
Maximal GH response (ATT) (mU/liter)[a]	18.5 [4–67]	16.5 [5–74]	21.3 [3–66]
Modified projected adult height (cm)	145.7 (5.7)	147.2 (4.9)	146.6 (5.6)
Target height (cm)	170.4 (6.6)	171.3 (6.0)	170.5 (5.6)
Karyotype			
45,X	16 (84%)	19 (95%)	16 (76%)
Other	3 (16%)	1 (5%)	5 (24%)

ATT, Arginine tolerance test.
[a] Geometric mean [range].

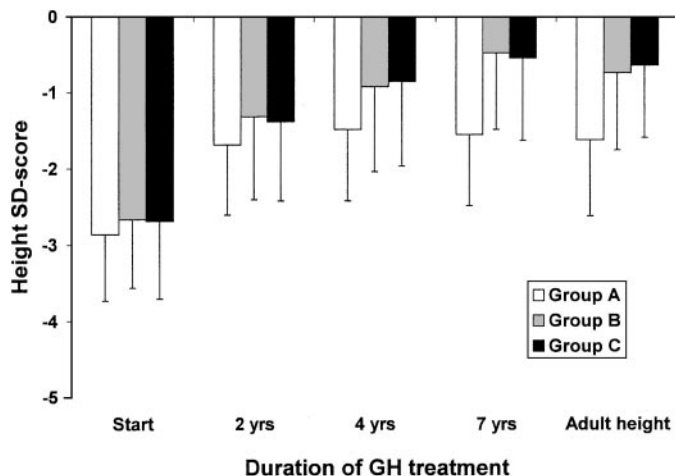FIG. 2. Height SD score for CA (ref. normal Dutch girls) during GH treatment for group A (□), group B (▧), and group C (■), respectively.

TABLE 2. Mean (SD) height data of 60 girls with TS after long-term GH treatment

	Group A (n = 19)	Group B (n = 20)	Group C (n = 21)
FH (cm)	157.6 (6.5) [143.1, 172.1]	162.9 (6.1)[a] [152.4, 176.2]	163.6 (6.0)[b] [153.3, 172.4]
FH SD score (reference, normal Dutch girls)	-1.6 (1.0) [-3.8, 0.5]	-0.7 (1.0)[a] [-2.6, 1.1]	-0.6 (1.0)[b] [-2.1, 0.9]
Height gain (cm) (FH minus mPAH)	11.9 (3.6) [2.8, 17.8]	15.7 (3.5)[a] [8.1, 20.4]	16.9 (5.2)[b] [7.2, 28.7]
Δ Height SD score (from start until FH)	1.2 (0.6) [-2, 2.0]	1.9 (0.5)[b] [0.9, 2.6]	2.1 (0.8)[b] [0.3, 3.6]
GH duration (yr)	8.9 (1.4) [6.5, 11.1]	8.3 (2.1) [5.5, 12.0]	8.7 (2.0) [5.3, 11.5]

Range is shown in *brackets*. Linear regression analysis with correction for age and height SD score at start (*vs.* group A): [a] $P < 0.01$; [b] $P < 0.001$.
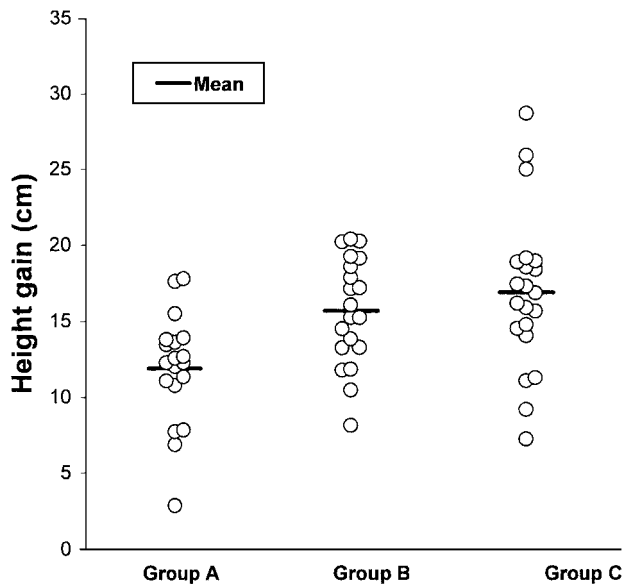
FIG. 3. Height gain (difference in centimeters between FH and modified projected adult height) for group A (n = 19), group B (n = 20), and group C (n = 21), respectively.

Prediction model for FH SD score and gain in height

A stepwise forward linear regression analysis resulted in a model using the predictor variables GH dose, height SD score (ref. normal girls) and CA at the start of treatment, and HV in the first year of GH treatment, accounting for 75.6% of the variation in FH SD score (residual SD 0.55). Table 3 shows the coefficients of the linear regression model. Variables, which showed a nonsignificant effect on FH SD score were IGF-I SD score and BA at the start of treatment, increase in IGF-I SD score in the first 18 months of treatment, increase in alkaline phosphatase in the first year of treatment, TH SD score, and karyotype (45,X, yes or no). The model equation was: FH SD score = $-2.29 + 0.80 \times$ height SD score at the start of treatment $+ 0.81 \times$ group C (yes = 1/no = 0) $+ 0.68 \times$ group B (yes = 1/no = 0) $+ 0.24 \times$ HV in the first year of treatment (cm) $+ 0.087 \times$ CA at the start of treatment (yr). To explore the effect of CA at the start of treatment on FH SD score, a partial correlation was made, controlling for GH dosage. The result was a significant negative correlation between FH SD score and CA (r = -0.30; $P < 0.05$).

When using the same predictor variables in a stepwise forward regression analysis to predict height gain (FH – mPAH in centimeters), the following model was obtained, after substitution of HV in the first year of treatment (centimeters) by HV SD score (ref. TS) and age at the start of treatment, and the addition of GH peak during ATT: height gain (cm) = 10.95 (SE, 2.58) $+ 1.15$ (0.47) $\times$ HV SD score in the first year of treatment $+ 4.01$ (1.18) $\times$ froup B (yes/no) $+ 5.55$ (1.16) group C (yes/no) $- 1.57$ (0.59) $\times$ height SD score at the start of treatment $- 1.04$ (0.28) $\times$ CA at the start of treatment (yr) $- 0.083$ (0.032) $\times$ GH peak (mU/liter). The model explained 45.6% of the variation in height gain (residual SD, 3.6 cm).
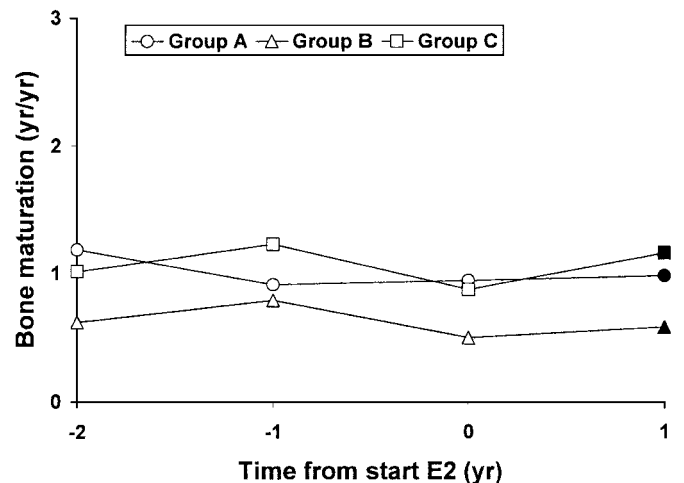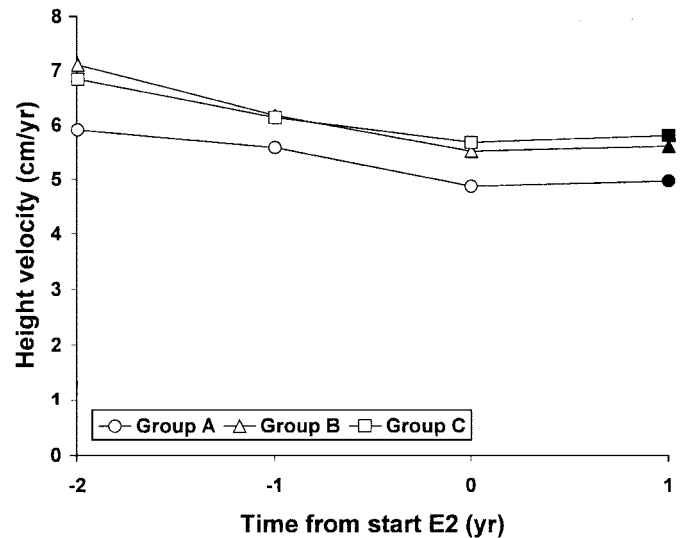

FIG. 4. HV (A) and bone maturation (B) before and after initiation of low dose estrogen (E2) treatment for group A (●), group B (▲), and group C (■) in girls who initiated estrogen treatment at age 12 yr (n = 47). The black signs indicate the HV and bone maturation after initiation of estrogen treatment.

IGF-I levels

The mean plasma IGF-I SD scores before, during, and 6 months after discontinuation of GH treatment are shown in Fig. 5. The mean plasma IGF-I SD score increased significantly from the start of GH treatment until 7 yr of GH treatment ($P < 0.0001$ for the whole group), from -2.3 ± 1.5 to 1.9 ± 0.8 for group A, from -1.4 ± 1.2 to 2.5 ± 0.9 for group B, and from -1.9 ± 1.4 to 2.7 ± 0.9 for group C. Although the increase from the start of treatment until 7 yr of GH treatment was not significantly different in groups A, B, and C, we did find a significantly higher IGF-I SD score at 7 yr of GH treatment in group C compared with group A ($P < 0.05$). After discontinuation of GH treatment, the IGF-I SD score decreased significantly ($P < 0.0001$ for the whole group) to a mean SD score of -0.6 ± 1.0 for group A, -0.1 ± 0.7 for group B, and -0.1 ± 0.9 for group C; the decrease was not significantly different between groups. The IGF-I SD score 6

TABLE 3. Variables in prediction model for FH SD score (n = 60)

Independent variable	Regression coefficient	SE	*P*
Height SD score at start[a]	0.80	0.09	<0.0001
Group C[b]	0.81	0.18	<0.0001
Group B[b]	0.68	0.18	<0.001
First year HV[c]	0.24	0.06	<0.01
Age at start	0.087	0.04	<0.05

Regression equation: FH SD score = −2.29 + 0.80 × height SD score at start + 0.81 × group C (yes = 1/no = 0) + 0.68 × group B (yes = 1/no = 0) + 0.24 × HV in first year + 0.087 × CA at start.
[a] Using references for normal girls.
[b] Group C, 1 = yes/0 = no; group B, 1 = yes/0 = no.
[c] In first year of GH treatment (centimeters per year).

months after discontinuation of GH treatment was not significantly different from zero (mean IGF-I level for same age and sex reference population) for groups B and C, but was less than zero for group A ($P < 0.05$).

Safety

No adverse events were detected that were considered GH related. Treatment was well tolerated. A previously published report using the same study group to describe glucose tolerance during long-term GH treatment showed no adverse effects on glucose levels (22). Furthermore, no significant differences in glucose and insulin levels between the GH dosage groups during long-term GH treatment were found (22). With the exception of two girls, glycosylated hemoglobin levels as well as leukocytes, hemoglobin, creatinine, aspartate aminotransferase, alanine aminotransferate, alkaline phosphatase, free T_4, and TSH levels remained within the normal range, and none of the children developed diabetes mellitus. Two girls had abnormal laboratory findings; one girl developed autoimmune hypothyroidism and was treated with thyroid hormone during the study, and another girl developed elevated levels of hepatic enzymes and hepatomegaly resulting from hepatic glandular malformations.

Discussion

In this paper we present FH results in 60 girls with TS after long-term GH treatment in three dosages. We show that when puberty is induced at a normal age, a GH dosage of 4 IU/m²·d (group A) in TS leads to a mean FH of 157.6 cm, which is equal to an SD score of −1.6 when using references for normal Dutch girls, whereas using 6 IU/m²·d (group B) leads to a significantly higher FH of 162.9 cm (SD score, −0.7). Administration of an even higher dosage of GH (8 IU/m²·d; group C) did not lead to a significant increase in attained FH compared with group B. As a result, 83% of the girls with TS reached a normal FH (FH SD score above −2), and 63% reached a FH within their target height range (TH ± 1.3 SD).

Our study shows that when GH was started at a mean age of 6.6 yr, the mean gain in FH [estimated by subtracting Lyon's predicted adult height, adjusted for Dutch girls with TS (mPAH), from attained FH] varied from 11.9 cm in group A to 16.9 cm in group C. The reason why previous studies reported a considerably lower gain in FH probably lies in the fact that they started GH treatment at an older age (8, 23, 24).
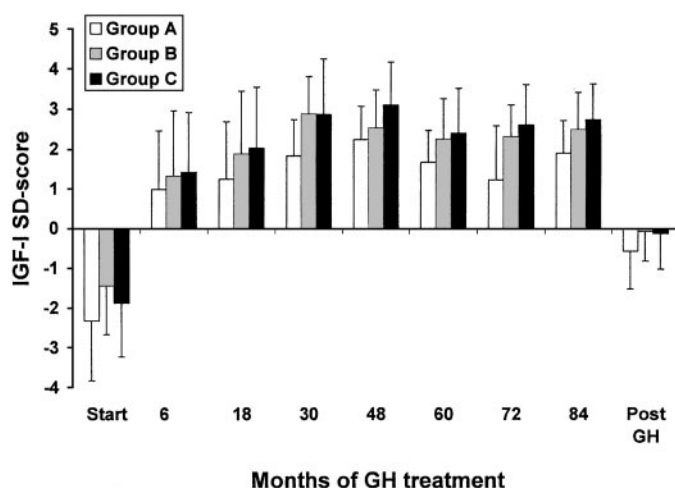

FIG. 5. IGF-I SD score during GH treatment for group A (□), group B (▨), and group C (■), respectively.

This is confirmed by the finding that other studies, starting GH treatment at a younger mean age, also showed a greater gain in FH (7, 25, 26). In addition, in our study we found that in a regression model containing HV SD score in the first year, height SD score and age at the start of treatment, GH peak, and GH dosage, a lower age at the start of treatment predicted a greater gain in FH. Another factor that predicted FH gain was the dosage of GH. Our study showed that using a dosage of 6 or 8 IU/m²·d, instead of 4 IU/m²·d, significantly increased gain in FH. Using a dose of 8 IU/m²·d, however, showed no advantage over a dose of 6 IU/m²·d for gain in FH. Our results were confirmed by two nonrandomized studies showing a dose-dependent increase in FH gain (27, 28).

Estrogen treatment in our study was initiated from the age of 12 yr to mimic normal pubertal development as much as possible. The result was breast development about 2 yr later than the 50th percentile in normal Dutch girls (13). In other studies most girls start at a later age (23, 28); some even start estrogen treatment at 15–16 yr (7, 25). In our opinion, however, based on our professional experience and research (29), it is important for the psychological well-being of girls with TS that puberty be induced at an age as close as possible to that experienced by their peers.

In addition, we show that starting a low dose of natural estrogen at a relatively young age did not have a negative effect on HV or bone maturation and, therefore, possibly on height gain. Other studies, in contrast, found a decrease in HV and an increase in bone maturation leading to a decrease in height gain (25, 30). The reason why our results are in conflict with these studies, however, might be that a higher dose of estrogen was used compared with that in our study. Another possible explanation might be that estrogen treatment was started after at least 4 yr of GH treatment. In these 4 yr, the height SD score for the whole group increased from −2.7 at the start of GH therapy to −0.9 at the start of estrogen treatment, showing that most of the catch-up growth had already occurred before estrogen treatment was initiated. Confirming this explanation, Reiter *et al.* (26) found that a longer duration of estrogen-free GH treatment strongly pre-

dicted a greater gain in near FH. Our results, therefore, suggest that if GH is started at a young age, FH will not be affected by early initiation of estrogen.

When analyzing the factors most likely to influence FH SD score, we found that a model containing the height SD score at the start of treatment using references for normal girls, GH dosage, first year height velocity (in centimeters), and age at start of treatment (in years) explained 76% of the variation in FH SD score outcome. To keep the model accessible for all clinicians, the peak GH level during arginine tolerance test, which is often not available in clinical practice, was not tested as a potential predictor, and HV was expressed in centimeters. The model can be used to decide which dosage to use by filling in the different variables. For example, a girl with TS, with a height SD score at the start of GH treatment of –3, an HV of 10 cm/yr after 1 yr of GH treatment (1 yr conventional dose of 4 IU/m²·d), and an age at the start of treatment of 6 yr would attain a final height SD score of –1.5 when the GH dose is not increased and an FH SD score of −0.8 or −0.7 when the GH dose is increased by 50% or 100%. Illustrating the effect of height SD score at the start of treatment, in a second example a similar girl with a height SD score at start of −4 would attain FH SD scores of –2.6, −1.9, and –1.7, respectively. In a third example, using the same characteristics as in the first example, changing the HV in the first year to 8 cm/yr would result in FH SD scores of –2.2, −1.6, and –1.4, respectively. As a fourth and last example, when the girl is 10 yr at the start of treatment, with a lower first year HV of 8.5 cm/yr (mean first year HV in our study for that age, as first year HV decreases with age), and a similar height SD score at the start of treatment, she would attain FH SD scores of –1.8, −1.1, and –1, respectively. Depending on one's goal, for instance achieving a normal FH or reaching the TH range, the GH dosage could be adjusted accordingly. Reasons why one might choose to increase the GH dosage are a low height SD score at the start of treatment and/or a low HV in the first year of treatment. Examples 2 and 3 show that these variables might lead to a lower FH SD score when using the conventional GH dose. Another reason for increasing the GH dosage is an older age at the start of treatment, shown in a separate correlation analysis between age at the start of treatment and FH SD score. In the model, however, we found a positive correlation between age at the start of treatment and FH SD score. This finding results from the adjustment for the other variables in the model, as both first year HV and height SD score at the start of treatment are negatively correlated with age at start ($r = -0.54$ and $r = -0.41$, respectively). In other words, older girls, due to their age, have a lower first year HV and height SD score at the start of treatment. Therefore, to explore the effect of age at the start of treatment in the model, not only age at the start of treatment, but also first year HV and height SD score should also be taken into account. Example 4 illustrates the relationship, showing a lower predicted FH SD score compared with the first example. A higher GH dosage, however, leads not only to a 50–100% increase in cost, but also to a higher IGF-I SD score, and the long-term effects of high IGF-I levels remain to be investigated (31, 32). In addition, we emphasize that although the model has a high prediction percentage, it does leave 24% to be explained by unknown factors. In addition, the predicted FH SD score has a large prediction interval (residual SD of 0.54).

In conclusion, GH treatment leads to a normalization of FH in most girls, even when puberty is induced at a relatively normal pubertal age. The optimal dosage to use depends on height and age at the start of treatment, and first year HV, although the very long-term safety of using a higher GH dosage remains to be investigated.

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