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Growth Hormone Treatment of Early Growth Failure in Toddlers with Turner Syndrome: A Randomized, Controlled, Multicenter Trial

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Context: Typically, growth failure in Turner syndrome (TS) begins prenatally, and height SD score (SDS) declines progressively from birth.

Objective: This study aimed to determine whether GH treatment initiated before 4 yr of age in girls with TS could prevent subsequent growth failure. Secondary objectives were to identify factors associated with treatment response, to determine whether outcome could be predicted by a regression model using these factors, and to assess the safety of GH treatment in this young cohort.

Design: This study was a prospective, randomized, controlled, open-label, multicenter clinical trial (Toddler Turner Study, August 1999 to August 2003).

Setting: The study was conducted at 11 U.S. pediatric endocrine centers.

Subjects: Eighty-eight girls with TS, aged 9 months to 4 yr, were enrolled.

Interventions: Interventions comprised recombinant GH (50 μg/kg·d; n = 45) or no treatment (n = 43) for 2 yr.

Main Outcome Measure: The main outcome measure was baseline-to-2-yr change in height SDS.

Results: Short stature was evident at baseline (mean length/height SDS = -1.6 ± 1.0 at mean age 24.0 ± 12.1 months). Mean height SDS increased in the GH group from -1.4 ± 1.0 to -0.3 ± 1.1 (1.1 SDS gain), whereas it decreased in the control group from -1.8 ± 1.1 to -2.2 ± 1.2 (0.5 SDS decline), resulting in a 2-yr between-group difference of 1.6 ± 0.6 SDS ($P < 0.0001$). The baseline variable that correlated most strongly with 2-yr height gain was the difference between mid-parental height SDS and subjects' height SDS ($r = 0.32$; $P = 0.04$). Although attained height SDS at 2 yr could be predicted with good accuracy using baseline variables alone ($R^2 = 0.81$; $P < 0.0001$), prediction of 2-yr change in height SDS required inclusion of initial treatment response data (4-month or 1-yr height velocity) in the model ($R^2 = 0.54$; $P < 0.0001$). No new or unexpected safety signals associated with GH treatment were detected.

Conclusion: Early GH treatment can correct growth failure and normalize height in infants and toddlers with TS. **(*J Clin Endocrinol Metab* 92: 3406–3416, 2007)**

TURNER SYNDROME (TS) is one of the most common genetic disorders, affecting approximately one in every 2000 live-born females (1, 2). Girls with TS have an absent or abnormal second sex chromosome and, without treatment, achieve an average adult height 20 cm shorter than their peers and their mid-parental height (3–8). Numerous clinical trials (9–14) and observational studies (15–17) have demonstrated GH-mediated improvements in height velocity and near-final or final (adult) height in girls with TS. However, the controlled clinical trials reported to date have focused on older girls, the mean age at study entry ranging from about 9–11 yr (10–14). No randomized, controlled clinical trials have specifically examined GH treatment in infants and toddlers with TS.

Although age at initiation of GH treatment is an important determinant of adult height in patients with TS (12–14, 18–20), and growth failure in girls with TS usually occurs in the first few years of life (8, 21–24), the initiation of GH in clinical practice is typically delayed, as evidenced by analyses of large U.S. and international postmarketing databases (25, 26). In the most recent analysis of U.S. data, GH was started at an average age of 9.0 ± 3.8 yr in the cohort of 471 patients enrolled between 1995 and 2000, representing a marginal change compared with the average age of 9.2 ± 3.5 yr for the 474 subjects enrolled over the preceding 10 yr (26). Similarly, age at GH initiation for girls with TS enrolled in a large international database between 1987 and 1999 was 10.1 ± 3.6

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Abbreviations: BMI, Body mass index; IGFBP-3, IGF-binding protein 3; MPH, mid-parental (target) height; SDS, SD score; TS, Turner syndrome.

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yr (25). Delayed initiation of therapy likely represents late diagnosis in some patients and failure to initiate therapy promptly after diagnosis in others. Such treatment delay has a number of potential negative consequences including progressive growth failure and delayed induction of puberty in an attempt to maximize adult height, which in turn may impact psychosocial function, bone mineralization, and cardiovascular health. Earlier diagnosis of TS is key to optimizing patient outcomes. However, in the absence of data from well-controlled clinical trials, it has been unknown whether early initiation of GH treatment in very young girls with TS can prevent subsequent growth failure. Therefore, the primary goal of this prospective, randomized, controlled, multicenter trial was to determine whether the ongoing growth failure that typically occurs in the first few years of life in girls with TS could be prevented or corrected by early GH treatment. In addition, to understand the variability of the GH treatment response, we evaluated factors associated with the magnitude of response and determined whether this could be predicted in a clinically useful way.

Subjects and Methods

Subjects were recruited from endocrine clinic and primary care referral populations, the Turner Syndrome Society of the United States and through website advertising (www.turner-syndrome-us.org; www.magicfoundation.org; www.hgfound.org; www.centerwatch.com). Criteria for study entry were: age 9 months to 4 yr; karyotype-proven TS; normal urinalysis, hemoglobin, and TSH; adequate thyroid hormone replacement for at least 6 months in those with hypothyroidism; and written informed consent from legal guardian(s). Exclusion criteria were presence of any Y-chromosomal component in the karyotype in subjects with gonads *in situ*, autosomal abnormality, concurrent treatment that might influence growth, and clinically relevant systemic illness. There were no specific eligibility criteria based on height or height velocity.

Study design

This prospective, randomized, controlled, 2-yr, open-label study conducted between August 1999 and August 2003 was approved by the ethics review boards of the 11 participating institutions in the United States and performed in accordance with the ethical principles of the Declaration of Helsinki. Eligible subjects were stratified into two groups based on age at study entry (9 months to 2.5 yr; >2.5 to 4 yr), and then, using a blinded phone-in process, were randomized in a 1:1 ratio to either a GH treatment group or a nontreatment control group. After a detailed baseline evaluation, subjects were followed at approximately 4-monthly intervals for 2 yr.

Treatment intervention

The GH group received daily sc injections of 50 μg/kg of GH (Humatrope; Eli Lilly and Co., Indianapolis, IN); the control group received no injections. Treatment compliance was assessed by review of study diaries and returned drug cartridges. Subjects were judged as compliant if they received at least 80% of their scheduled GH injections.

Efficacy measures

The primary outcome measure was linear growth, as measured by change in SD score (SDS) for length or height (depending on age), from baseline to 2 yr. A height gain of at least 0.5 SDS was designated as clinically significant. Age-appropriate measurements were obtained at each visit for length, using an infant-measuring box (children <2 yr of age or older children for whom accurate standing measurements could not be obtained), and/or height, using a standard wall-mounted stadiometer (children older than 2 yr). Because of the overlap in U.S. normative datasets for infancy and childhood, both length and height were measured for girls aged between 2 and 3 yr. If a child had both length and height measurements at the same study visit, the length measurement was used in the analyses.

Length or height SDS values (hereafter referred to as height SDS even if length was measured) were calculated on the basis of data for age-matched girls from the U.S. Centers for Disease Control (27). Mid-parental (or target) height (MPH) was calculated as follows: (father's height − 13 cm + mother's height)/2 (28) and converted to SDS using normative height data for women at 20 yr of age (27).

Laboratory data and radiology

Standard hematological and clinical chemistry tests were performed at baseline. Serum IGF-I, IGF-binding protein-3 (IGFBP-3), and bone turnover markers (N-telopeptide X and amino-terminal propeptide of type I collagen) were measured at baseline, 4 months, 1 yr, and 2 yr. IGF-I and IGFBP-3 assays were performed by Esoterix Endocrinology (Calabasas Hills, CA); SDS were calculated using Esoterix's data for healthy controls. Bone turnover markers were measured at the University of Connecticut (Hartford, CT). Measurements of TSH and FSH were performed using standard assays at baseline, 1 yr, and 2 yr [FSH results have been reported (29)]. For girls with nonmosaic karyotypes whose families consented, parental origin of the X chromosome (maternal *vs.* paternal) was determined by DNA microsatellite analysis (Greenwood Genetics, Greenwood, SC). All analyses were performed at central laboratories. Bone age x-rays (left wrist and hand) obtained at baseline, 1 yr, and 2 yr were read according to the standards of Greulich and Pyle (30) by two independent readers blinded to all subject information and reported as the average of the two readings.

Safety measures

Safety was assessed at each visit based on reported adverse events, detailed history, and physical examinations. In addition, because girls with TS are at increased risk for a variety of health problems, information regarding specific, relevant medical conditions was obtained by targeted collection on the case report forms. Furthermore, because of the increased risk of otitis media and hearing loss in girls with TS, a thorough assessment of ear disease, including measurements of middle ear function by tympanometry, was performed at each visit, and formal audiometry was performed annually.

Statistical methods

The primary efficacy analysis, prespecified in the protocol, was conducted on the baseline-to-2 yr change in height SDS for all subjects who had measurements at both time points, using an ANOVA model with treatment group and baseline age group as explanatory variables. The between-treatment group differences in height SDS at baseline and at each post-baseline visit were also analyzed using this model. A secondary analysis was performed with data for all subjects who had at least one post-baseline measurement, including those who did not complete the study, using a repeated-measures mixed model to assess between-group differences for change in height SDS from baseline to each post-baseline visit. The model used a heterogeneous variance structure such that the variance was allowed to differ within each age group. Weight SDS and body mass index (BMI) (kg/m^2) at baseline, at each visit, and at the 2-yr endpoint and the changes in these variables from baseline to each post-baseline visit were compared between treatment groups using the ANOVA and repeated-measures models described above.

For analyses of changes in height SDS, one-sided tests were used with the significance level set at 0.05. All other analyses of efficacy variables were conducted using two-sided tests with the significance level set at 0.05.

To determine factors contributing to the variability of response to GH, correlations between the outcome variables (2-yr height SDS and baseline-to-2-yr change in height SDS) and baseline or treatment-related variables were examined using the Pearson correlation coefficient. In addition to variables with significant univariate correlations, a number of clinically relevant baseline and on-study variables were then used to develop multiple linear regression models to determine whether an individual subject's response to GH (2-yr height SDS or baseline-to-2-yr change in height SDS) could be predicted in a clinically useful manner. Model selection was based on the complexity of the model, assessment

of model bias (Mallow's Cp statistic), and the predictive performance [predicted residual sum of squares (PRESS) statistic] of the model. For comparison, models were also developed for the untreated group (data not shown).

Serious adverse events, treatment-emergent adverse events, and laboratory data were summarized for all subjects who entered the study.

Analyses were performed using SAS software (version 8.2; SAS Institute, Inc., Cary, NC). Data are reported as mean ± 1 SD, unless noted otherwise.

Results

Eighty-nine girls aged 9 months to 4 yr (24.0 ± 12.1 months) were randomized to a nontreatment control group (n = 44) or a GH treatment group (n = 45) (Table 1). After study entry, one control subject was found to have a 46,XX karyotype; her data were excluded from the efficacy analyses but are included in the safety analyses. Karyotype distribution was as follows: 45,X karyotype was present in 29 of 43 (67%) control subjects and 27 of 45 (60%) GH-treated subjects; 45,X/46,XX karyotype was present in 7 of 43 (16%) control subjects and 7 of 45 (16%) GH-treated subjects; the remaining subjects 7 of 43 (16%) controls and 11 of 45 (24%) GH-treated subjects] had a variety of other karyotypes. Of 35 subjects with nonmosaic karyotypes whose families agreed to participate in testing for parental origin of the X chromosome, 29 (83%) had maternal X chromosomes and six (17%) had paternal X chromosomes.

Seventy-nine of the 89 randomized subjects completed the 2-yr study (control n = 38 of 44, including the subject with 46,XX karyotype; GH n = 41 of 45). Reasons for discontinuation were as follows: for the control group, parents' decisions (n = 2), scheduling problems (n = 1), request for GH treatment (n = 2), and lost to follow-up (n = 1); for the GH group, relocation (n = 1) and lost to follow-up (n = 3). Compliance with GH treatment was generally excellent; 95% of subjects received at least 80% of their scheduled injections. On average, subjects received 95% of their total scheduled injections, but there was substantial interindividual variability in overall compliance (range, 75–100%).

GH corrected growth failure and restored height to the normal range

Early GH treatment corrected growth failure and promoted catch-up growth in this cohort of under-4-yr-old girls with TS; the control group had progressive growth failure, with height falling by an additional 0.5 ± 0.5 SDS from −1.8 ± 1.1 (baseline) to −2.2 ± 1.2 (2 yr), whereas mean height of the GH group increased by 1.1 ± 0.6 SDS, from −1.4 ± 1.0 (baseline) to −0.3 ± 1.1 (2 yr) (Fig. 1). Thus, the between-group difference for change in height SDS after 2 yr was 1.6 ± 0.6 ($P < 0.0001$). This analysis was performed on data from the 78 subjects with karyotype-proven TS who completed the 2-yr study. A sensitivity analysis using a repeated-measures mixed model with data for all 87 subjects who had at least one post-baseline measurement (including nine subjects who discontinued before study completion) also demonstrated a significantly greater post-baseline increase in height SDS for the GH group [between-group difference (least squares mean ± SE), 1.03 ± 0.09 SDS; $P < 0.0001$].

The GH treatment effect was rapid; the between-group difference in height SDS was significant by 4 months and increased progressively (Fig. 1). Treatment effect was also reflected by the significantly greater first- and second-year height velocity and height velocity SDS in the GH-treated group (height velocity: first-year control, 8.0 ± 2.4 cm/yr, and first-year GH, 11.7 ± 2.4 cm/yr, $P < 0.0001$; second-year control, 5.5 ± 1.8 cm/yr, *vs.* second-year GH, 8.4 ± 1.6 cm/yr, $P < 0.0001$; height velocity SDS: first-year control, −0.83 ± 0.95, *vs.* first-year GH, 1.75 ± 1.25, $P < 0.0001$; second-year control, −1.63 ± 1.29, *vs.* second-

TABLE 1. Baseline and endpoint data by treatment group

Variable	Baseline			2-yr endpoint		
	Nontreatment control group (n = 43)	GH treatment group (n = 45)	All (n = 88)	Nontreatment control group (n = 37)	GH treatment group (n = 41)	*P* value at endpoint
Chronological age (yr)	1.97 ± 1.01	1.98 ± 1.01	1.98 ± 1.00	4.03 ± 1.03	4.03 ± 1.05	0.9944
Bone age (yr)[a]	1.88 ± 0.96	1.95 ± 0.89	1.92 ± 0.92	3.38 ± 1.11	4.24 ± 1.35	0.0033
Bone age − chronological age (yr)	−0.14 ± 0.42	−0.06 ± 0.56	−0.10 ± 0.50	−0.64 ± 0.80	0.21 ± 0.96	<0.0001
Length/height (cm)	77.6 ± 8.7	78.9 ± 8.6	78.3 ± 8.6	91.9 ± 7.2	99.5 ± 7.6	<0.0001
Length/height SDS	−1.76 ± 1.07	−1.42 ± 1.00	−1.59 ± 1.04	−2.16 ± 1.22	−0.34 ± 1.10	<0.0001
MPH (cm)[b]	164.4 ± 4.7	164.4 ± 5.0	164.4 ± 4.9	164.1 ± 4.9	164.7 ± 4.9	0.5608
MPH SDS[b]	0.16 ± 0.73	0.17 ± 0.77	0.17 ± 0.75	0.12 ± 0.76	0.22 ± 0.76	0.5607
Weight (kg)	9.92 ± 2.47	10.35 ± 2.28	10.14 ± 2.37	13.81 ± 2.50	16.62 ± 2.86	<0.0001
Weight SDS	−1.77 ± 1.46	−1.31 ± 1.18	−1.54 ± 1.34	−1.37 ± 1.36	0.20 ± 1.06	<0.0001
BMI (kg/m^2)	16.24 ± 1.29	16.48 ± 1.37	16.36 ± 1.33	16.24 ± 1.29	16.72 ± 1.70	0.1724
Head circumference (cm)[c]	46.7 ± 2.1	47.2 ± 2.4	46.9 ± 2.3	49.9 ± 1.4	51.1 ± 1.5	0.0004
Head circumference SDS[c]	−0.14 ± 1.19	0.09 ± 1.05	−0.02 ± 1.12	0.30 ± 0.99	1.17 ± 1.03	0.0004
IGF-I SDS[d]	−0.39 ± 0.95	−0.25 ± 0.85	−0.31 ± 0.89	−0.69 ± 0.84	1.26 ± 0.72	<0.0001
IGFBP-3 SDS[d]	−0.83 ± 1.05	−0.66 ± 1.08	−0.74 ± 1.06	−1.12 ± 1.13	0.97 ± 0.94	<0.0001

The data exclude one subject who was found after study entry to have a 46,XX karyotype. Data shown are mean ± 1 SD. There were no significant differences between treatment groups at baseline.

[a] Baseline bone age missing for two subjects in each group.

[b] Father's height missing for one GH subject at both baseline and endpoint.

[c] Baseline data missing for one subject in each group; one control subject had an erroneous value at baseline, so the value was not used; endpoint data missing for two control subjects.

[d] Baseline data missing for eight control subjects and three GH-treated subjects; endpoint data missing for four control subjects and seven GH subjects.

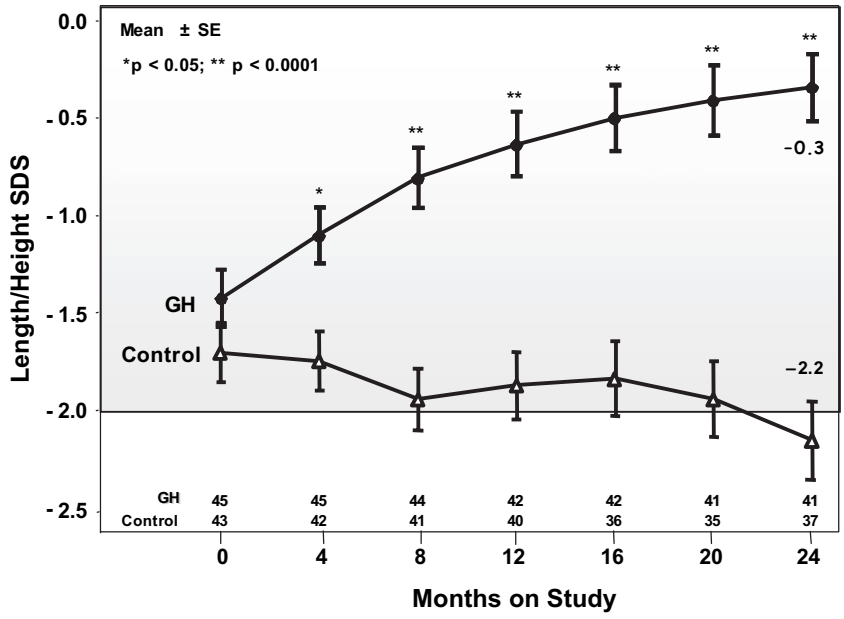

FIG. 1. Length/height SDS for the nontreatment control group (*open symbols*) and the GH treatment group (*filled symbols*) during the 2-yr study. Between-group difference at endpoint was 1.6 ± 0.6 SDS ($P < 0.0001$).

year GH, 0.70 ± 1.11, $P < 0.0001$). Total 2-yr height gain was 13.6 ± 3.5 cm for the control group compared with 20.4 ± 3.3 cm for the GH group ($P < 0.001$).

The GH treatment effect was also evident when the heights of control and GH-treated subjects were compared with U.S. standards (27). Control subjects had progressive decreases across the height percentile channels, whereas the heights of all but three of the GH-treated subjects were restored within the normal channels (Fig. 2). Two-year GH-induced height gain was between 0.0 and +1.0 SDS for 21 of 41 (51%) subjects, between +1.0 and +2.0 SDS for 14 of 41 (34%), and more than +2.0 SDS for five of 41 (12%). At the 2-yr time point, only 7% of GH-treated subjects remained below −2.0 SDS (~2.3rd percentile); in contrast, 57% of the controls were below −2.0 SDS at 2 yr ($P < 0.0001$). In parallel with the increases in height SDS, GH-treated subjects had significantly greater increases in weight SDS than did control subjects. However, because of the significantly greater height gains in the GH group, there was negligible between-group difference in BMI (Table 1).

Effect of GH treatment on bone age

Baseline bone age was similar to chronological age in this young cohort (bone age of 1.92 ± 0.92 yr *vs.* chronological age

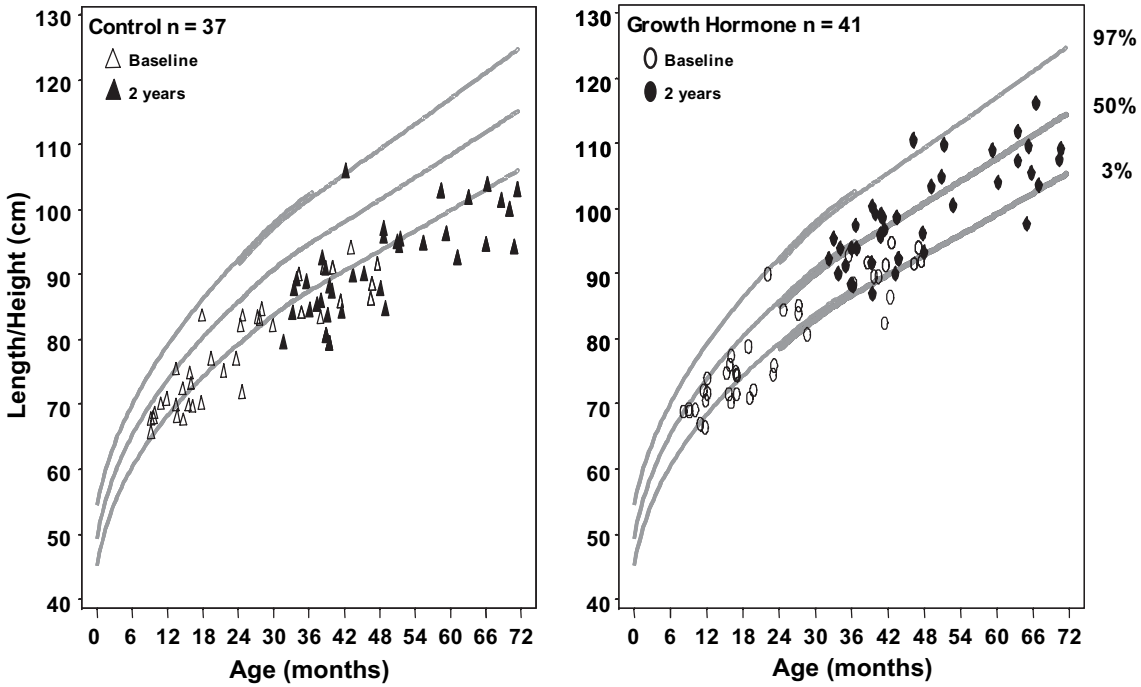

FIG. 2. Baseline (*open symbols*) and 2-yr (*filled symbols*) length/height measurements for the nontreatment control group (*left*) and the GH treatment group (*right*), relative to the 3rd, 50th, and 97th percentiles for the U.S. female reference population (27).

of 1.98 ± 1.00 yr; Table 1). During the 2-yr study, bone age fell behind chronological age for control subjects, whereas there was a small advance for GH-treated subjects (bone age minus chronological age at 2 yr: control, −0.64 ± 0.80 yr; GH, 0.21 ± 0.96 yr).

Effect of GH treatment on IGF-I and IGFBP-3

Mean IGF-I SDS was −0.31 ± 0.89 at baseline for the total subject group (Table 1). Baseline-to-2 yr changes in IGF-I SDS were −0.09 ± 0.87 for controls and 1.53 ± 0.93 for the GH group. Although IGF-I values were above +2.0 SDS for 37% of GH-treated subjects on at least one post-baseline measurement, no subject had elevated IGF-I SDS at all visits (Fig. 3A). GH-related changes in IGFBP-3 paralleled IGF-I changes, such that there was a significant correlation between on-treatment values for the two peptides at each post-baseline measurement (at 4 months, r = 0.63, $P < 0.0001$, n = 39; at 1 yr, r = 0.80, $P < 0.0001$, n = 36; at 2 yr, r = 0.59, $P = 0.0004$, n = 31; Fig. 3B). At 2 yr, only one subject had a value that fell within the hypothetical risk profile of an IGF-I SDS in the upper tertile with an IGFBP-3 SDS in the lower tertile (31–35).

Factors affecting GH response

GH treatment corrected growth failure and promoted catch-up growth in the treated group as a whole; however, the magnitude of the individual treatment effect varied. Changes in height SDS ranged from a decline of 0.6 SDS in one girl whose treatment compliance was among the lowest to gains of more than 2.0 SDS in five girls who started treatment quite early (between 15 and 27 months) and were more than 90% compliant. There was a modest, but significant,

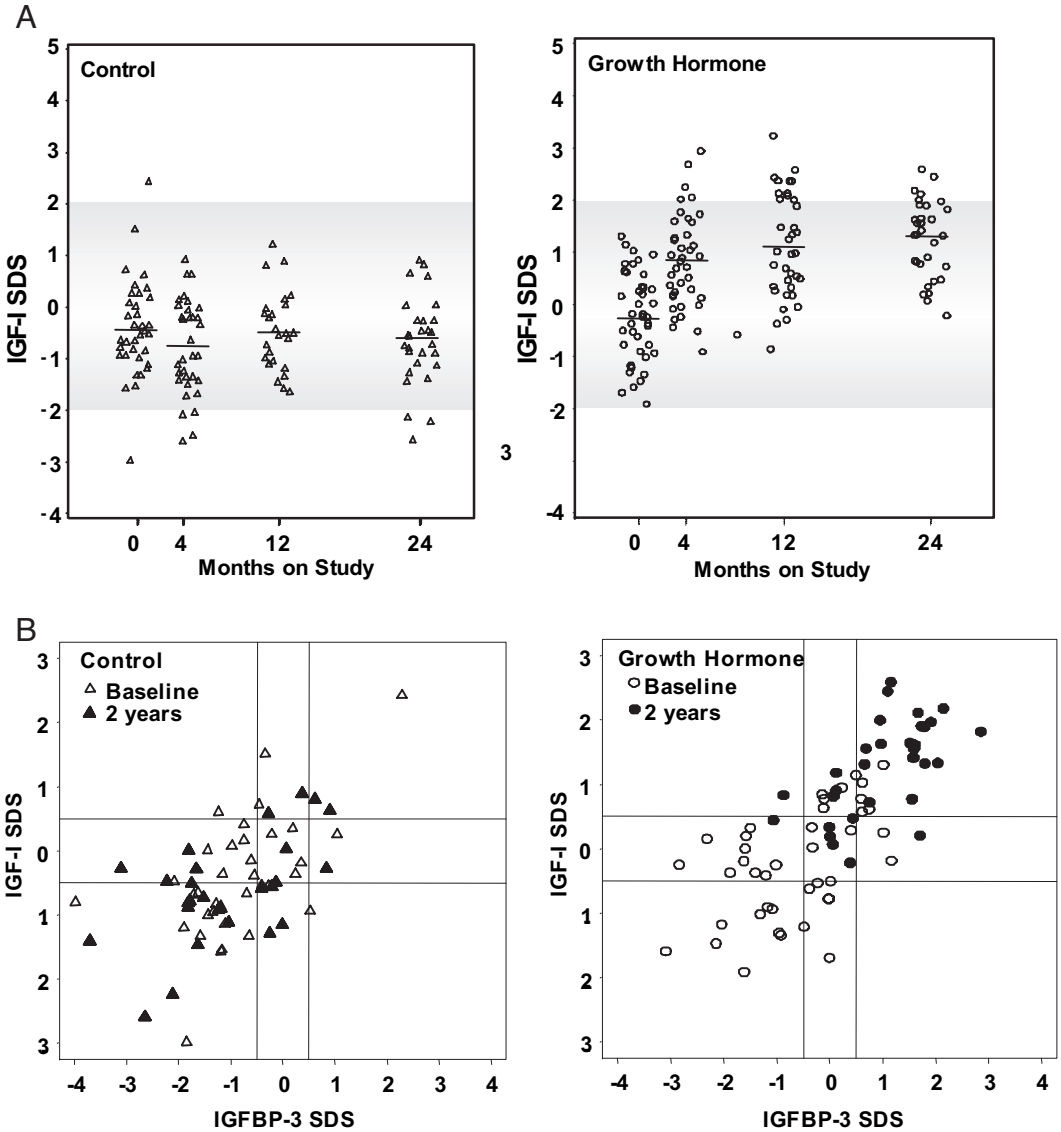

FIG. 3. A, Baseline and on-study values for IGF-I SDS for control group (*left*) and the GH group (*right*). *Horizontal lines* within the clusters of symbols at each time point represent the mean value for the group. B, relationship between IGF-I SDS and IGFBP-3 SDS at baseline and 2 yr. Data are presented by tertiles for subjects in the control group (*left*) and the GH group (*right*). For the control group at 2 yr, r = 0.57, $P < 0.0017$; for the GH group at 2 yr, r = 0.59, $P < 0.0004$.

correlation between 2-yr height SDS change and average injection compliance rate (n = 40, r = 0.33, $P = 0.04$).

Although baseline height SDS differed somewhat among karyotype groups (45,X: −1.55 ± 1.02; 45,X/46,XX: −0.93 ± 1.35; other: −1.42 ± 0.65), the difference was not statistically significant ($P = 0.35$), and karyotype had no significant effect on outcome (Fig. 4). The average 2-yr height gain was somewhat lower for the 45,X group (primarily because of the poorly compliant subject described above), but height gains were significant for each karyotype group (45,X: 0.95 ± 0.58 SDS; 45,X/46,XX: 1.26 ± 0.53 SDS; other: 1.30 ± 0.77 SDS), without a significant between-group difference. Similarly, there was no effect of parental origin of the X chromosome (maternal *vs.* paternal) on height gain (maternal: 0.87 ± 0.74 SDS, n = 10; paternal: 1.07 ± 0.25 SDS, n = 4; $P = 0.62$). GH-induced catch-up growth was considered clinically relevant (≥0.5 SDS) in most subjects [34 of 41 (83%)] and within each karyotype group [45,X: 21 of 26 (81%); 45,X/46,XX: seven of seven (100%); other: six of eight (75%)].

To determine other factors associated with magnitude of response, we evaluated correlations between baseline and on-study variables and outcomes (both 2-yr height SDS and baseline-to-2-yr height SDS gain; Tables 2 and 3). The baseline variable most strongly associated with 2-yr height SDS was baseline height SDS (r = 0.83, $P < 0.0001$), which explained almost 70% of the variance in attained height at 2 yr. In contrast, the variable that correlated most strongly with baseline-to-2-yr height SDS gain was the difference between MPH SDS and baseline height SDS, which explained about 10% of the variance (r = 0.32, $P = 0.04$), suggesting that subjects with the greatest height deficit relative to their genetic height potential may have greater catch-up growth. Not surprisingly, the on-study variable that correlated most strongly with height gain was first-year height velocity, which explained about 15% of the variance in 2-yr height SDS gain (r = 0.39, $P = 0.01$).

Prediction of response to GH

To predict treatment outcomes, a number of regression models were developed using various combinations of baseline and on-study variables. Significant models were developed for height SDS at 2 yr and 2-yr height SDS gain that may be useful depending on clinical circumstances and available data (Table 4). The most powerful predictor of height SDS at 2 yr was baseline height SDS, and all multivariate models required inclusion of baseline height SDS for significance. Inclusion of one or more additional baseline variables alone or in combination, such as the difference between bone age and chronological age, MPH SDS, IGF-I SDS, and IGFBP-3 SDS improved the predictive power of the models modestly (R^2 values of 0.72–0.75 for two-variable models). In addition, two robust models were developed using four baseline variables each ($R^2 = 0.81$, $P < 0.0001$; Table 4).

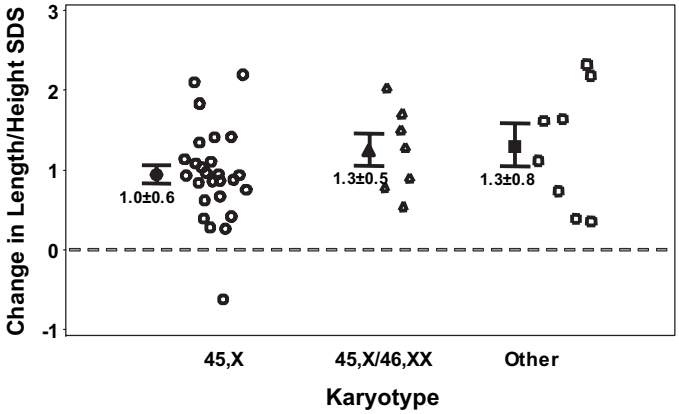

FIG. 4. Individual changes in length/height SDS from baseline to 2 yr (*open symbols*). Data are presented by karyotype group; *solid symbols* represent mean ± SE. There were no significant differences between the karyotype groups.

Not surprisingly, inclusion of one or more variables reflecting initial treatment response (such as 4-month or 1-yr height velocity and 4-month or 1-yr IGF-I or IGFBP-3 SDS) substantially improved the predictive power of the models, such that R^2 values up to 0.86 were obtained with four-variable models. Notably, the models using 4-month treatment variables were as robust as those that included 1-yr variables, indicating that the initial treatment response is a good predictor of 2-yr response.

The models were less accurate in predicting 2-yr height SDS gain than actual height SDS, and no model was significant without inclusion of height velocity.

Safety analyses

No new or unexpected safety signals associated with GH treatment were detected, and no subject discontinued because of an adverse event. Serious adverse events were reported for four of 44 (9%) girls in the control group (one subject each was hospitalized for surgical repair of an atrial septal defect, croup/bronchiolitis, gastroenteritis, and dehydration) and four of 45 (9%) girls in the GH group (one subject each was hospitalized for gastroenteritis/dehydration, bacterial pneumonia, persistent bleeding after tonsillectomy, and hypoxemia after adenoidectomy). Treatment-emergent adverse events (events or conditions that began or worsened after study entry) were reported for 43 of 44 (98%) of controls and 42 of 45 (93%) of GH-treated girls. Many of these events were related to ear disorders. There was no detrimental effect of GH treatment on frequency of episodes of otitis media, rates of ear tube insertion, middle ear function, or hearing. Most other events reported with a high frequency were typical childhood illnesses (*e.g.* fevers, infections, colds, and gastrointestinal disorders), considered unlikely to have been related to GH treatment. There were no significant changes or between-group differences in serum TSH.

Discussion

GH therapy was approved for use in girls with TS by the U.S. Food and Drug Administration in 1996 on the basis of four studies that included girls whose average ages at study entry ranged from 9.1–10.3 yr (10–12, 14). Since then, the efficacy of GH treatment for improving short- and long-term growth and adult height in school-aged girls with TS has become even better established (9, 13, 15–17, 36–38). Although the Food and Drug Administration approval did not mandate a specific chronological age for initiation of GH therapy in TS, pediatric endocrinologists seem to have been reticent to start GH early. Al-

TABLE 2. Correlations between baseline and on-study variables and height SDS at 2 yr in the GH-treated group, ranked by correlation coefficient

Factor	Sample size for analysis	Correlation coefficient R	*P* value
Significant			
Baseline variables			
Length/height SDS	41	0.83	<0.0001
Weight SDS	41	0.63	<0.0001
MPH SDS minus baseline length/height SDS	40	−0.52	0.0006
Father's height SDS	40	0.47	0.0020
MPH SDS	40	0.46	0.0025
IGFBP-3 SDS	38	0.45	0.0046
Bone age minus chronological age	39	0.40	0.0112
On-study variables			
1-yr height velocity (cm/yr)	41	0.51	0.0007
2-yr IGF-I SDS	34	0.49	0.0031
2-yr IGFBP-3 SDS	34	0.48	0.0044
4-month IGFBP-3 SDS	37	0.44	0.0058
1-yr height velocity SDS	41	0.38	0.0135
4-month IGF-I SDS	37	0.38	0.0216
1-yr IGFBP-3 SDS	38	0.36	0.0264
Not significant			
Baseline variables			
Mother's height SDS	41	0.28	0.08
Chronological age	41	−0.23	0.15
IGF-I SDS	38	0.16	0.33
Bone age	39	−0.02	0.89
On-study variables			
Baseline-to-1-yr change in IGF-I SDS	35	0.33	0.05[a]
1-yr IGF-I SDS	38	0.32	0.05[a]
Baseline-to-2-yr change in IGF-I SDS	31	0.30	0.10
Baseline-to-4-month change in IGF-I SDS	36	0.22	0.19
Baseline-to-4-month in IGFBP-3 SDS	36	0.12	0.49
Baseline-to-2-yr change in IGFBP-3 SDS	31	0.09	0.62
First 4-month height velocity (cm/yr)	41	0.08	0.61
Baseline-to-1-yr change in IGFBP-3 SDS	35	0.06	0.74
First 4-month height velocity SDS	41	−0.05	0.78
Baseline-to-2-yr change in collagen N-terminal propeptide	35	−0.01	0.96

[a] Actual *P* values = 0.051, therefore not significant.

though the reticence in specific cases may be due to factors such as family fears of giving injections, pressing medical/surgical issues, or significant developmental/behavioral concerns, it is likely that the major cause has been the absence of efficacy and safety data in very young girls. This is unfortunate, because growth failure may be quite profound in infancy and the toddler years. Indeed, in one study of longitudinal data for under-8 yr olds with TS, height of 50% of the girls fell below the fifth percentile of the population standard at a mean age of 18 months (22). Although GH treatment data have been reported for small numbers of preschool-aged girls (13, 36, 39), no randomized, nontreatment controlled study has evaluated the role of GH in correcting the growth failure that typically occurs in the first few years of life in girls with TS; the study reported here addresses this gap. In this large-scale, multicenter trial, 2 yr of GH treatment initiated between 9 months and 4 yr of age prevented ongoing growth failure and restored height to within the normal range for 93% of girls before 6 yr of age. Compared with girls who received no treatment, whose height SDS continued to decline, GH-treated girls demonstrated rapid, highly significant increases in height velocity and height SDS. As a result, after 2 yr, there was a 1.6 SDS (6.8 cm) between-group difference in height gain, and mean height of the GH-treated group was very close to average for the general population of the same age (−0.3 SDS).

Early normalization of height has a number of potential benefits for young girls with TS, including prevention of stature-related juvenilization and mascotism, improvement in peer-group integration, reduction of the gap that must be bridged between height at treatment initiation and genetic target height, and the opportunity to initiate estrogen replacement at a physiologically appropriate age (11, 18, 19, 37, 38).

Many studies of GH treatment in girls with TS have established the importance of age at treatment initiation for long-term height gain (12–18, 39). Furthermore, the magnitude of the prepubertal height gain appears to be a key determinant of overall height attainment (17). No previous randomized trial has studied patients as young as our cohort, although a single-arm, observational study in 29 girls with TS aged between 1.4 and 5.9 yr (mean 4.3 yr) provides some comparative data (39). Height gain after 2 yr was about 1.0 SDS, similar to the 1.1 SDS gain in our 2-yr study. However, the absence of a control group in the observational study likely underestimated the efficacy of GH treatment because the overall impact of GH treatment represents the combined effect of preventing ongoing growth failure (evidenced by further height SDS decline in our controls) and promoting catch-up growth. Thus the overall 2-yr treatment effect (prevention of ongoing growth failure plus catch-up growth) in our study was 1.6 SDS.

Although we found no correlation between age at start of GH treatment and height gain (likely because of limited age

TABLE 3. Correlations between baseline and on-study variables and change in height SDS from baseline to 2 yr in the GH-treated group, ranked by correlation coefficient

Factor	Sample size for analysis	Correlation coefficient R	*P* value
Significant			
Baseline variables			
MPH SDS minus baseline length/height SDS	40	0.32	0.04
On-study variables			
1-yr height velocity SDS	41	0.67	<0.0001
2-yr IGF-I SDS	34	0.52	0.0017
First 4-month height velocity SDS	41	0.52	0.004
First 4-month height velocity (cm/yr)	41	0.41	0.008
Baseline-to-2-yr change in IGF-I SDS	31	0.40	0.03
1-yr height velocity (cm/yr)	41	0.39	0.01
2-yr IGFBP-3 SDS	34	0.36	0.037
Not significant			
Baseline variables			
Father's height SDS	40	0.26	0.10
Bone age minus chronological age	39	0.26	0.11
Length/height SDS	41	−0.21	0.19
Bone age	39	0.21	0.20
MPH SDS	40	0.16	0.33
IGFBP-3 SDS	38	0.11	0.52
IGF-I SDS	38	0.08	0.65
Weight SDS	41	−0.06	0.69
Mother's height SDS	41	−0.04	0.82
Chronological age	41	0.03	0.86
On-study variables			
Baseline-to-2-yr change in collagen N-terminal propeptide	35	0.30	0.08
Baseline-4 month change in IGFBP-3 SDS	36	0.30	0.08
4-month IGFBP-3 SDS	37	0.29	0.09
Baseline-to-2-yr change in IGFBP-3 SDS	31	0.29	0.11
1-yr IGFBP-3 SDS	38	0.28	0.09
Baseline-to-1-yr change in IGFBP-3 SDS	35	0.24	0.16
4-month IGF-I SDS	37	0.23	0.17
Baseline-to-1-yr change in IGF-I SDS	35	0.18	0.31
Baseline-to-4-month change in IGF-I SDS	36	0.15	0.39
1-yr IGF-I SDS	38	0.14	0.41

range and treatment duration), age and bone age were nevertheless significant factors in a number of height prediction models developed in this study, as also reported by others (17, 25). Age dependency of GH responsiveness (40) is hypothesized to reflect the decline in proliferative capacity of growth plate chondrocytes with increasing age—the concept of programmed growth plate senescence (41, 42).

Whereas initial reports indicated normal linear growth during the preschool years in girls with TS (3, 4), more recent studies demonstrate early-onset growth failure in the first few months and years of life (8, 21–24). Given this finding, guidelines for care of individuals with TS, which previously recommended that "initiation of GH therapy should be considered as soon as a patient with TS has dropped below the fifth percentile of the normal female growth curve" (43), have been revised, and the updated guidelines state that "treatment with GH should be considered as soon as growth failure (decreasing height percentiles) is demonstrated and its potential risks and benefits have been discussed with the family" (44). Unfortunately, because many patients with TS are not diagnosed until mid-childhood, adolescence, or even adulthood (20, 45–47), the opportunity to improve height remains limited for many patients. Consequently, a concerted effort is required to enable earlier diagnosis for girls with TS (18, 24, 45, 47, 48).

Although the overall efficacy of GH treatment in TS is now well established, there is significant variation in individual patient responsiveness to treatment (12–16, 36, 37). Consequently, the clinician considering GH treatment for a child with TS has limited ability to provide the family with expectations for potential treatment outcome. To address this clinical challenge, investigators have evaluated factors that correlate with the GH treatment response. In addition to age at treatment initiation and GH dose, other baseline factors reported to influence outcome positively include MPH (reflecting genetic height potential), baseline height and weight SDS, bone age delay (13, 17, 25), presence of a retained maternal (*vs.* paternal) X chromosome (49), and presence of the short (exon 3-deleted) form of the GH receptor (50). Using these findings, various models have been developed to predict height achieved or gained after GH treatment (13, 15, 17, 25). Notably, although baseline variables are adequate for modest prediction of initial treatment response, prediction of response after the first year requires inclusion of a variable that reflects initial response (*e.g.* first-year height velocity or change in height velocity from baseline) (13, 25). Similarly, we found that the models had substantially greater predictive power when a variable reflecting initial treatment response was included. The key conclusion from these analyses is that although it may be possible to predict a portion of the response before initiating treatment, even the best baseline-variable-only models cannot predict response to GH with the degree of accuracy necessary for clinical decision making on an individual patient basis. An additional key point from these regression analyses is that baseline height SDS had negligible

TABLE 4. Prediction models for height SDS at 2 yr and change in height SDS from baseline to 2 yr

Model no.	Models for dependent variable	R^2	PRESS	*P* value
Dependent variable, height SDS at 2 yr				
Using baseline variables only				
1	0.89 + (0.88 × BH SDS)	0.70	16.01	<0.0001
2	0.75 + (0.82 × BH SDS) + (0.23 × MPH SDS)	0.72	15.43	<0.0001
3	0.87 + (0.85 × BH SDS) + (0.03 × [BA − CA])	0.75	14.32	<0.0001
4	0.96 + (0.83 × BH SDS) + (0.03 × [BA − CA]) + (0.10 × IGFBP-3 SDS)	0.80	11.95	<0.0001
5	0.89 + (0.80 × BH SDS) + (0.03 × [BA − CA]) + (0.13 × MPH SDS) + (0.12 × IGFBP-3 SDS)	0.81	12.17	<0.0001
6	0.85 + (0.84 × BH SDS) − (0.03 × BA) + (0.04 × CA) + (0.10 × IGFBP-3 SDS)	0.81	12.48	<0.0001
Using baseline and 4-month on-study variables				
1	0.13 + (0.91 × BH SDS) + (0.06 × 4-month HV)	0.74	14.50	<0.0001
2	0.71 + (0.85 × BH SDS) + (0.21 × 4-month IGF-I SDS)	0.77	12.30	<0.0001
3	−0.27 + (0.89 × BH SDS) + (0.24 × 4-month IGF-I SDS) + (0.07 × 4-month HV)	0.84	9.32	<0.0001
4	−0.71 + (0.92 × BH SDS) + (0.02 × BA) + (0.24 × 4-month IGF-I SDS) + (0.08 × 4-month HV)	0.86	8.31	<0.0001
Using baseline and 1-yr on-study variables				
1	0.76 + (0.83 × BH SDS) + (0.18 × 1-yr IGFBP-3 SDS)	0.73	14.69	<0.0001
2	−0.86 + (0.79 × BH SDS) + (0.14 × 1-yr HV)	0.77	13.00	<0.0001
3	−2.40 + (0.79 × BH SDS) + (0.03 × BA) + (0.21 × 1-yr HV)	0.84	9.64	<0.0001
4	−2.45 + (0.75 × BH SDS) + (0.03 × BA) + (0.20 × 1-yr HV) + (0.15 × 1-yr IGFBP-3 SDS)	0.86	8.54	<0.0001
Dependent variable, change in height SDS from baseline to 2 yr				
Using baseline variables only				
1	0.74 + (0.19 × [MPH SDS − BH SDS])	0.10	14.80	0.0442
Using baseline and 4-month on-study variables				
1	−0.12 + (0.08 × 4-month HV) + (0.20 × 4-month IGF-I SDS)	0.35	9.20	0.0006
2	−0.65 + (0.02 × BA) + (0.09 × 4-month HV) + (0.22 × 4-month IGF-I SDS)	0.41	7.95	0.0010
3	−0.38 + (0.15 × [MPH SDS − BH SDS]) + (0.07 × 4-month HV) + (0.25 × 4-month IGF-I SDS)	0.45	8.32	0.0002
Using baseline and 1-yr on-study variables				
1	−1.53 + (0.03 × BA) + (0.16 × 1-yr HV) + (0.11 × 1-yr IGFBP-3 SDS)	0.38	10.88	0.0011
2	−2.45 − (0.25 × BH SDS) + (0.03 × BA) + (0.20 × 1-yr HV) + (0.15 × 1-yr IGFBP-3 SDS)	0.54	8.54	<0.0001

The models may be interpreted as follows: the first number in each model is the intercept; numbers in *parentheses* with explanatory variables are the parameter estimates for each variable. The variable parameter estimate represents the change of the dependent variable when the explanatory variable changes by one unit given that the other explanatory variables do not change. BA, Bone age; BH, baseline height; CA, chronological age; HV, height velocity; PRESS, predicted residual sum of squares (indicates predictive performance of the model; the smaller number, the better the predictive power of the model).

influence on the magnitude of the height gain, indicating that the opportunity for GH-induced catch-up growth is similar irrespective of height at treatment initiation. Therefore, a GH treatment trial is probably warranted in most patients with TS who have evidence of growth failure, whether in infancy or later in childhood.

In summary, this randomized, controlled clinical trial demonstrates that the growth failure typical of early childhood in girls with TS can be corrected when GH treatment is initiated by four years of age. These findings underscore the importance of early diagnosis of TS and prompt referral to a pediatric endocrinologist for assessment of the many physical and developmental problems that may be associated with this condition, including growth failure. In general, the younger the patient is at GH initiation, the smaller the height deficit to be bridged and the faster height is normalized. Early restoration of height close to average in this unique patient cohort should mitigate potential detrimental effects of short stature during childhood and allow for age-appropriate initiation of feminization. However, because the long-term efficacy and safety of such early treatment remains to be determined, a 10-yr study extension is underway, following the original cohort to adult height.

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