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Growth Hormone Is Effective in Treatment of Short Stature Associated with Short Stature Homeobox-Containing Gene Deficiency: Two-Year Results of a Randomized, Controlled, Multicenter Trial

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Background: The short stature homeobox-containing gene, *SHOX*, located on the distal ends of the X and Y chromosomes, encodes a homeodomain transcription factor responsible for a significant proportion of long-bone growth. Patients with mutations or deletions of *SHOX*, including those with Turner syndrome (TS) who are haploinsufficient for *SHOX*, have variable degrees of growth impairment, with or without a spectrum of skeletal anomalies consistent with dyschondrosteosis.

Objective: Our objective was to determine the efficacy of GH in treating short stature associated with short stature homeobox-containing gene deficiency (SHOX-D).

Design and Methods: Fifty-two prepubertal subjects (24 male, 28 female; age, 3.0–12.3 yr) with a molecularly proven *SHOX* gene defect and height below the third percentile for age and gender (or height below the 10th percentile and height velocity below the 25th percentile) were randomized to either a GH-treatment group (n = 27) or an untreated control group (n = 25) for 2 yr. To compare the GH treatment effect between subjects with SHOX-D and those with TS, a third study group, 26 patients with TS aged 4.5–11.8 yr, also received GH. Between-group comparisons of first-year and second-year height velocity, height SD score, and height gain (cm) were performed using analysis of covariance accounting for diagnosis, sex, and baseline age.

Results: The GH-treated SHOX-D group had a significantly greater first-year height velocity than the untreated control group (mean ± SE, 8.7 ± 0.3 *vs.* 5.2 ± 0.2 cm/yr; $P < 0.001$) and similar first-year height velocity to GH-treated subjects with TS (8.9 ± 0.4 cm/yr; $P = 0.592$). GH-treated subjects also had significantly greater second-year height velocity (7.3 ± 0.2 *vs.* 5.4 ± 0.2 cm/yr; $P < 0.001$), second-year height SD score (−2.1 ± 0.2 *vs.* −3.0 ± 0.2; $P < 0.001$) and second-year height gain (16.4 ± 0.4 *vs.* 10.5 ± 0.4 cm; $P < 0.001$) than untreated subjects.

Conclusions: This large-scale, randomized, multicenter clinical trial in subjects with SHOX-D demonstrates marked, highly significant, GH-stimulated increases in height velocity and height SDS during the 2-yr study period. The efficacy of GH treatment in subjects with SHOX-D was equivalent to that seen in subjects with TS. We conclude that GH is effective in improving the linear growth of patients with various forms of SHOX-D. **(*J Clin Endocrinol Metab* 92: 219–228, 2007)**

THE SHORT STATURE homeobox-containing gene, *SHOX*, discovered during the search for genes underlying the growth deficit of Turner syndrome (TS), is located in the pseudoautosomal region 1 on the distal end of the X and Y chromosomes at Xp22.3 and Yp11.3 (1, 2). Because genes in pseudoautosomal region 1 do not undergo X inactivation, healthy individuals express two copies of the *SHOX* gene, one from each of the sex chromosomes in both 46,XX and 46,XY individuals. The *SHOX* gene encodes a homeodomain transcription factor expressed during early fetal life in developing skeletal tissue of the radius and ulna, the tibia and distal femur, and the first and second pharyngeal arches (3). The protein is specifically expressed in the growth plate in hypertrophic chondrocytes undergoing apoptosis and appears to play an important role in regulating chondrocyte differentiation and proliferation (4, 5).

Because they lack all or part of their second X chromosome, individuals with TS have only a single copy of the *SHOX* gene. This state of *SHOX* haploinsufficiency appears to be substantially responsible for the average 20-cm height deficit in untreated women with TS, relative to their mid-parental height and relative to the average height of adult women of the same ethnic background (6, 7), although other factors such as aneuploidy or chromosomal imbalance may contribute (8–10). In addition to its role underlying the growth deficit of TS, *SHOX* haploinsufficiency, or short stature homeobox-containing gene deficiency (SHOX-D), is also the primary cause of short stature in most patients with Léri-Weill dyschondrosteosis, also known as Léri-Weill syndrome (LWS) (11–13), a pseudoautosomal dominant condition with greater penetrance in females than males (11, 14). Furthermore, as reported in the original paper detailing the cloning of the gene (2), and confirmed by a number of sub-

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Abbreviations: IGFBP-3, IGF-binding protein 3; ISS, idiopathic short stature; LWS, Léri-Weill syndrome; SDS, SD score; SHOX-D, short stature homeobox-containing gene deficiency; TS, Turner syndrome.

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sequent studies, *SHOX* mutations and deletions are also found in patients with an unremarkable short stature phenotype, often referred to as idiopathic short stature (ISS) (15–17). Although initially diagnosed with ISS for lack of etiological explanation, some of these SHOX-D patients have subtle signs of skeletal disproportion and should be excluded from the nonspecific diagnosis of ISS (18).

Mutations or deletions of the *SHOX* gene are associated with a broad spectrum of phenotypic effects, ranging from short stature without dysmorphic signs to profound mesomelic skeletal dysplasia, a form of short stature characterized by disproportionate shortening of the middle (mesial) segments of the upper and lower limbs (*i.e.* the forearms and lower legs) (8, 17). This skeletal anomaly is typically observed in patients with LWS (11, 19) and to a lesser degree in patients with TS. The features include bowing of the forearms and lower legs, cubitus valgus, Madelung deformity (dinner fork-like wrist) or partial dislocation of the ulna at the wrist and elbow, short fourth metacarpals, and high-arched palate. These clinical findings are usually accompanied by a number of characteristic radiological signs (7, 14, 20). The rare homozygous (or compound heterozygous) form of SHOX-D, referred to as Langer mesomelic dysplasia, is characterized by extreme dwarfism, profound mesomelia, and severe limb deformity (21–24). On the basis of a number of screening studies, SHOX-D appears to be a relatively frequent cause of short stature. Deletions or mutations of the *SHOX* gene have been reported in approximately 70% of patients with LWS and approximately 2–15% of children with the clinical phenotype of ISS (15–17). Overall, SHOX-D appears to have a greater prevalence than TS, which occurs in 1 in 2000 live female births (25), equivalent to approximately one in 4000 total births.

GH treatment of short stature associated with TS is well established on the basis of over 20 yr of clinical trial data (26–28) including a randomized, controlled study to adult height (29). However, experience with GH treatment in patients with SHOX-D is limited to case reports and small, uncontrolled studies (14, 20, 30, 31). Therefore, this study aimed to evaluate the efficacy and safety of GH treatment in subjects with isolated SHOX-D in a randomized, controlled clinical trial. In addition, given the similarity in the pathogenesis of the growth disorder between subjects with TS and those with SHOX-D, this study also sought to compare the growth response to GH treatment across these two conditions.

Subjects and Methods

Subjects

Subjects were invited to participate in genetic screening for this study if they fulfilled the following entry criteria: chronological age at least 3 yr and prepubertal (males, genital stage Tanner 1 and testes $\leq$ 2 ml; females, breast stage Tanner 1), height less than third percentile of the local reference range or height less than 10th percentile with height velocity less than 25th percentile, bone age less than 10 yr for boys and less than 8 yr for girls or less than 9 yr for TS, no GH deficiency or GH resistance, no chronic disease, and no known growth-influencing medications.

Study design

This study was a 2-yr, three-arm, randomized, controlled, open-label clinical trial conducted at 33 study sites in 14 countries (see *Acknowledgments* for details). After stratification by sex and according to presence or absence of LWS, 52 prepubertal subjects (24 male, 28 female) with confirmed SHOX-D were randomized on a one-to-one basis, either to a GH-treatment group (n = 27) or to an untreated control group (n = 25). The primary objective of the study was to evaluate the effect of GH treatment on first-year height velocity in subjects with SHOX-D. The effect of GH treatment on adult height in these subjects will be determined after completion of an ongoing long-term, open-label extension study. Given the similar pathogenesis of short stature in TS and SHOX-D, the secondary objective of the study was to compare the GH treatment effect between subjects with SHOX-D and those with TS. Therefore, the third study arm enrolled 26 subjects with TS to GH treatment only. Treated subjects in both the SHOX-D and TS groups received a daily sc injection of 50 μg/kg GH [Humatrope (somatropin, rDNA origin); Eli Lilly & Co., Indianapolis, IN).

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committees of the participating institutions. Written informed consent was obtained from the subjects' parent(s) or legal guardian(s) before conducting any study-related procedure.

Molecular/genetic analyses for SHOX gene defects

DNA samples from eligible children (n = 1608) were screened for a *SHOX* gene defect by one of two methods: 1333 samples were screened by PCR analysis for the presence of three microsatellites in the vicinity of the *SHOX* locus (CA-SHOX, CAII, and DXYS233), and 275 samples were screened by analysis of a number of exonic and intronic single-nucleotide polymorphisms. Samples that showed homozygosity for all screened markers (microsatellites or single-nucleotide polymorphisms) were analyzed by fluorescence *in situ* hybridization using a *SHOX* gene-containing cosmid probe. Presence of only a single *SHOX* signal confirmed deletion of one *SHOX* allele. The DNA of all 1608 individuals was also screened for single-nucleotide mutations by denaturing HPLC using a WAVE DNA-Fragment Analysis System (Transgenomic Inc., Cheshire, UK). Evidence of a DNA sequence alteration on denaturing HPLC was confirmed by DNA sequencing using a MegaBACE sequencer with the DYEnamic ET terminator Cycle Sequencing Kit (Amersham Biosciences, Piscataway, NJ). The diagnosis of TS was confirmed by karyotype analysis at individual study sites. Female subjects with a partial deletion of the short arm of the X chromosome were classified as having SHOX-D rather than TS if the deletion was located distal to the gene for ocular albinism (OA1) at the junction between Xp22.2 and Xp22.3.

Clinical and biochemical assessments

Enrolled subjects were evaluated at baseline for standing height and preexisting conditions. Subsequent evaluations were performed at 3 and 6 months and then at 6-monthly intervals for the remainder of the 2-yr study. Left hand and wrist x-rays for bone age were obtained at baseline and 1 and 2 yr, and the films were assessed centrally according to the standards of Greulich and Pyle (32). Routine blood chemistry, hematology, fasting blood glucose, TSH, and free T_4 were obtained at baseline and first year. Blood was drawn for measurement of IGF-I and IGF-binding protein 3 (IGFBP-3) concentrations at baseline, at 3 and 6 months, and at 6-monthly intervals thereafter. The analyses were performed at a central laboratory, using previously reported methods (33).

In addition to standard reporting of serious adverse events, data were collected by the use of specific directed questions on the case report forms for the following potentially GH-related conditions (in alphabetical order): arthralgia, benign intracranial hypertension, edema, gynecomastia (males), hyperglycemia, hypoglycemia, hypothyroidism, increase in size of cutaneous nevi, neoplasia, recurrent otitis media, scoliosis, and slipped capital femoral epiphysis.

Statistical analysis

To account for differences in sex and age of the subjects, a number of variables were analyzed after conversion to SD scores (SDS). Because the

majority of subjects originated from central European countries, height SDS was calculated using a central European reference (34). Bone age SDS was calculated as (bone age − chronological age)/SD of bone age corresponding to chronological age using the Greulich and Pyle (32) standards. Height velocity SDS was calculated based on the standards of Preece (35). Body mass index was calculated as weight (kilograms)/height (meters) squared and was converted to SDS by the method of Cole (36). Sex- and age-adjusted IGF-I SDS and IGFBP-3 SDS values were calculated using the reference values established in the central laboratory (37).

The primary aim of this study was to test the hypothesis that first-year height velocity of GH-treated subjects with SHOX-D would be greater than that of untreated subjects. The primary analysis, prespecified in the protocol, was an analysis of covariance for GH-treated *vs.* untreated subjects with first-year height velocity as the response variable and treatment group, diagnosis (LWS *vs.* ISS), sex, and baseline age as explanatory variables. One subject who discontinued with no post-baseline height data was excluded from efficacy analyses; all subjects were included in safety analyses.

Baseline variables were compared between groups using ANOVA for continuous variables and Fisher exact tests for categorical variables. Additional analyses were performed using ANOVA for between-group differences in height velocity SDS, height gain in centimeters, height SDS, bone age, and bone age SDS at various time points among all subjects, subjects with the ISS phenotype, and subjects with the LWS phenotype. We also investigated whether or not the impact of treatment on first-year height velocity depended on the values of the following variables: sex, baseline age, diagnosis (LWS *vs.* ISS), baseline height SDS, target height SDS, and baseline IGF-I. This was evaluated by examining the interaction term in a model with terms for treatment, variable, and interaction. Laboratory variables were analyzed using ANOVA models for between-group comparisons. Except where otherwise stated, results from statistical models are presented as least-squares mean ± SE with two-sided statistical significance level set at 0.05.

Results

Molecular defects in the SHOX gene

During the screening phase of the study, *SHOX* gene deletions or mutations were detected in 68 subjects (34 with ISS phenotype, 32 with LWS phenotype, and two with unspecified phenotype); of these, 52 subjects were subsequently enrolled in this GH intervention study. Of these 52 subjects, 34 (65.4%; 16 untreated control, 18 GH-treated) had a complete deletion of the *SHOX* gene, four (7.7%; two in each group) had partial gene deletions, and 14 (26.9%; seven in each group) had point mutations. Of the 14 subjects with point mutations, three had a nonsense mutation (one with E61X, two with R195X), 10 had a missense mutation (Q112P, K116E, L132V, Y141D, R168W, R168L, A170P, R173H, and two with X226bR), and one subject had an insertion (insH229-L232). Missense mutations were judged to be clinically relevant if they fulfilled any of the following criteria: *in vitro* testing confirmed loss of function (L132V, R168W, A170P, and R173H) (38), a severe phenotype (LWS) was present (L132V, R168L, R173H, and X226bR), the short stature phenotype segregated with the genotype in pedigree analysis (Q112P, L132V, Y141D, A170P, R168W, and insH229-L232), or the mutation had previously been described in the literature as clinically relevant (L132V, R168W, A170P, and R173H) (14, 23, 39). Amino acids L132, R168, and R173 are conserved in human, chicken, and fish (http://www4.ncbi.nlm.nih.gov/).

Baseline data

There were no significant differences among the three study groups for most of the demographic and auxological parameters (age, bone age, height, *etc.*) at baseline (Table 1). However, target height SDS was lower in subjects with SHOX-D than in those with TS, probably reflecting the pseudoautosomal dominant inheritance of SHOX-D in many of these subjects. There were no significant differences between the groups with SHOX-D (GH-treated *vs.* untreated control) for the proportion of male *vs.* female subjects or for the proportion of subjects in each group with the LWS *vs.* ISS phenotype.

Response to GH treatment

Fifty-one of 52 randomized subjects with SHOX-D, and all 26 enrolled subjects with TS, completed the 2-yr GH treatment period. One untreated control subject with SHOX-D discontinued the trial within the first 3 months, based on the subject's decision. Height velocity and height SDS improved markedly in response to GH in the treated SHOX-D and TS groups but changed minimally in the untreated control SHOX-D group (Fig. 1, A and B). As shown in detail in Table 2, the GH-treated SHOX-D group had significantly greater first-year height velocity than the untreated control group and similar first-year height velocity to GH-treated subjects with TS. GH-treated subjects with SHOX-D also had significantly greater second-year height velocity, second-year height SDS, and second-year height gain than untreated subjects with SHOX-D and similar values for these parameters

TABLE 1. Baseline characteristics

Variable	Untreated SHOX-D (n = 25)	GH-treated SHOX-D (n = 27)	GH-treated TS (n = 26)	*P* value
Female/male (%)	52/48	56/44	100/0	
LWS/ISS (%)	56/40	44/56		0.689
Chronological age (yr)	7.5 ± 2.7	7.3 ± 2.1	7.5 ± 1.9	0.914
Bone age (yr)	6.6 ± 2.8	6.5 ± 2.0	6.7 ± 1.6	0.928
Bone age − chronological age	−1.0 ± 0.9	−0.8 ± 0.8	−0.8 ± 1.0	0.809
Bone age SDS	−1.2 ± 1.1	−1.0 ± 1.0	−1.0 ± 1.1	0.641
Height SDS	−3.3 ± 1.0	−3.3 ± 0.8	−3.7 ± 0.9	0.111
Target height SDS	−1.3 ± 1.0	−1.5 ± 0.9	−0.6 ± 1.4	0.013
Body mass index SDS	0.2 ± 0.9	0.6 ± 0.9	0.2 ± 0.7	0.147
IGF-I SDS	−0.8 ± 1.0	−0.9 ± 1.0	−1.1 ± 1.2	0.521
IGFBP-3 SDS	0.6 ± 1.3	0.1 ± 1.1	−0.3 ± 1.4	0.058

Data are expressed as the mean ± SD. Efficacy variables presented represent pretreatment values.

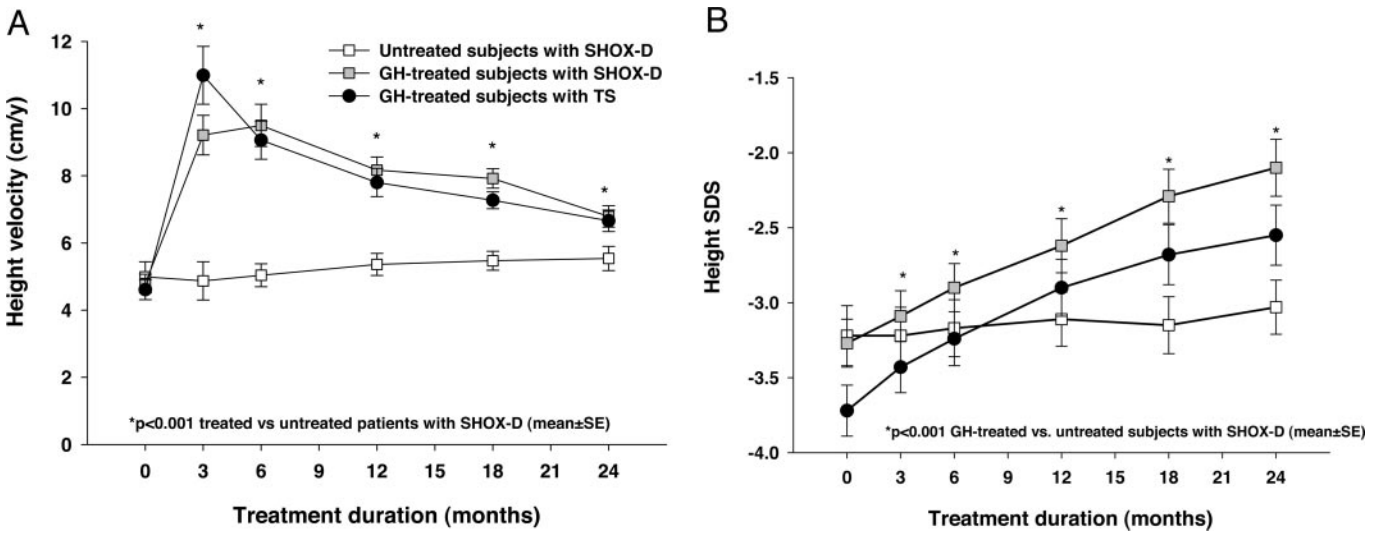

FIG. 1. Treatment group means (± SE) for annualized height velocity (cm/yr) (A) and height SDS (B) in patients with SHOX-D or TS.

compared with GH-treated subjects with TS. Figure 2 demonstrates on an individual subject basis that these improvements in growth rate in the GH-treated subjects resulted in a progressive increase in height SDS; at the end of the second-year study period, 41% of GH-treated subjects with SHOX-D and 31% of subjects with TS had achieved height within the normal range for age and gender (>−2.0 SDS), whereas this was the case for only one of the untreated subjects with SHOX-D who started with a height SDS of more than −2 and remained there. The analyses of body proportions showed some improvement of mesomelia during the 2-yr study period; however, there was no significant difference between GH-treated and untreated subjects either in the whole groups or in subjects with LWS in particular (data not shown). Moreover, the frequency of Madelung deformity did not increase in any of the study groups during the 2-yr period.

Subgroup analyses

To evaluate any possible sexual dimorphism in treatment response, the height velocity of GH-treated subjects with SHOX-D was analyzed for males *vs.* females for those subjects who had not entered puberty by the end of the second year to avoid any confounding effect of a sex steroid-induced growth spurt. Although the first-year height velocity was somewhat greater for males (9.3 ± 0.5 cm/yr) than for females (8.4 ± 0.5 cm/yr), the baseline to second-year change in height velocity was very similar. Furthermore, the treatment effect was similar for girls with SHOX-D and those with TS because the difference in second-year height velocity between these subgroups (SHOX-D females, 7.4 ± 0.3 cm/yr; TS, 6.8 ± 0.2 cm/yr) was not significant. The GH treatment effects in the subgroups of subjects with the ISS or the LWS phenotypes were significant except for height SDS in subjects with LWS (Table 3). Overall, the treatment effect appears somewhat greater in subjects with the ISS phenotype compared with subjects with LWS; however, the differences were not statistically significant. For subjects with SHOX-D, there was no significant interaction (with respect to first-year height velocity) between the treatment and the following baseline variables: sex, age, diagnosis (LWS *vs.* ISS), height SDS, target height SDS, and IGF-I.

Effects of GH on skeletal maturation and pubertal development

Although the effect of GH treatment on various height parameters in subjects with SHOX-D was substantial, there was no evidence that this was the result of a significant effect on skeletal maturation. Baseline bone age was delayed by

TABLE 2. Growth parameters at baseline and 1 and 2 yr on study

	SHOX-D UnTx		SHOX-D GH		TS GH		*P* value (SHOX-D): GH *vs.* UnTx	*P* value: SHOX-D GH *vs.* TS GH
	n	Mean ± SE	n	Mean ± SE	n	Mean ± SE		
Baseline HV (cm/yr)	14	5.0 ± 0.5	18	4.8 ± 0.3	19	4.6 ± 0.3	0.721	0.769
Baseline HV SDS	10	−1.0 ± 0.6	12	−1.2 ± 0.3	7	−0.9 ± 0.3	0.605	0.806
Baseline Ht SDS	24	−3.2 ± 0.2	27	−3.3 ± 0.2	26	−3.7 ± 0.2	0.822	0.069
First-year HV (cm/yr)	24	5.2 ± 0.2	27	8.7 ± 0.3	26	8.9 ± 0.4	<0.001	0.592
First-year HV SDS	22	−0.7 ± 0.2	25	3.0 ± 0.3	26	2.7 ± 0.3	<0.001	0.663
First-year Ht SDS	24	−3.1 ± 0.2	27	−2.6 ± 0.2	26	−2.9 ± 0.2	<0.001	0.374
Second-year HV (cm/yr)	24	5.4 ± 0.2	27	7.3 ± 0.2	26	7.0 ± 0.2	<0.001	0.238
Second-year HV SDS	22	−0.4 ± 0.1	27	2.3 ± 0.3	26	1.9 ± 0.3	<0.001	0.262
Second-year Ht SDS	24	−3.0 ± 0.2	27	−2.1 ± 0.2	26	−2.6 ± 0.2	<0.001	0.698
2-yr Ht gain (cm)	24	10.5 ± 0.4	27	16.4 ± 0.4	26	15.7 ± 0.6	<0.001	0.244

Data are expressed as the mean ± SE. Ht, Height; HV, height velocity; UnTx, untreated subjects.

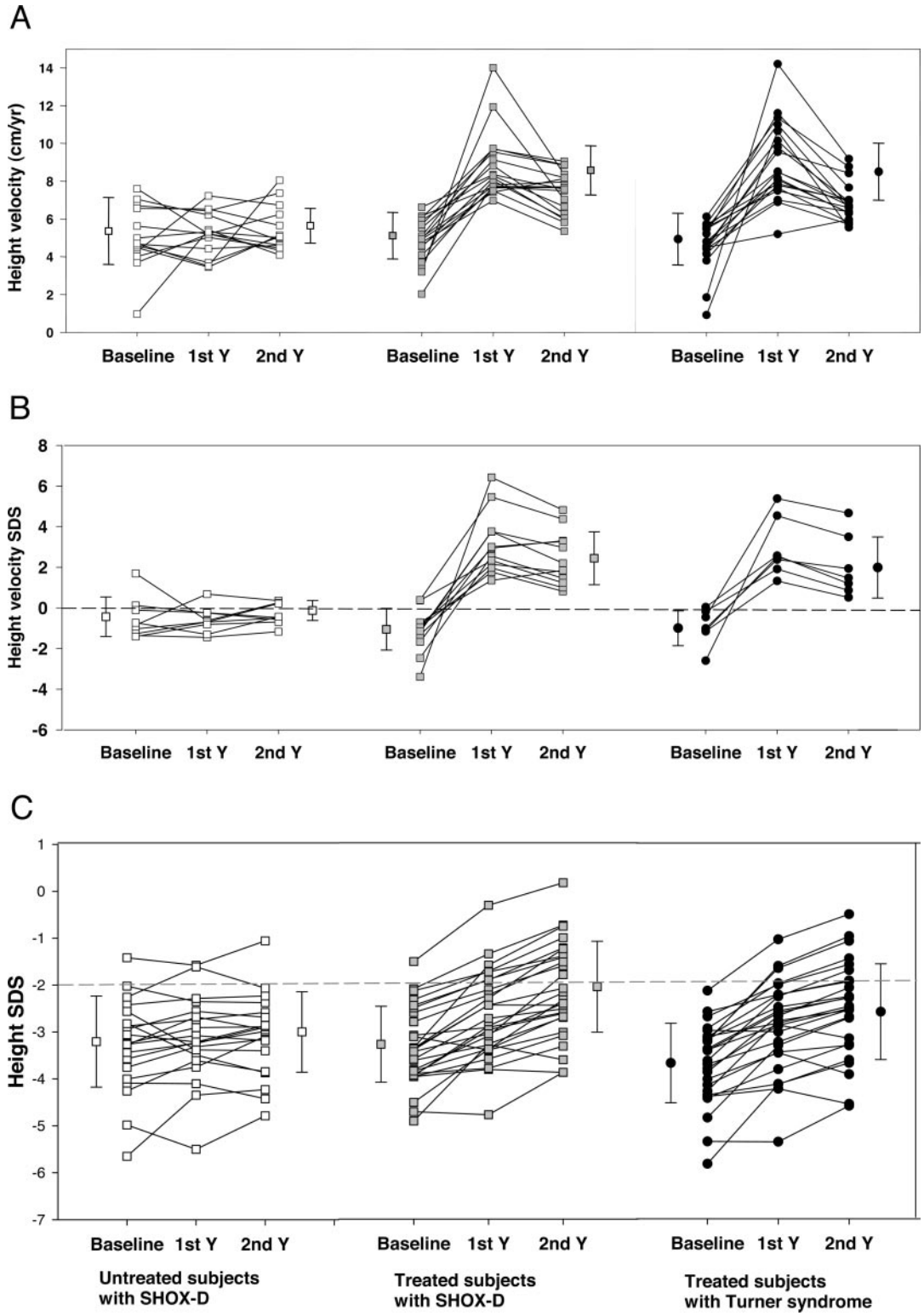

FIG. 2. Group means (± SE) and individual data for height velocity (cm/yr) (A), height velocity SDS (B), and height SDS (C) by treatment groups in patients with SHOX deficiency or TS.

about 1 yr in all groups, and although there was a trend toward greater catch-up of bone age in the GH-treated SHOX-D group than the untreated control group (respective means, 1.34 ± 0.07 and 1.16 ± 0.09 yr; $P = 0.161$), the groups overlapped significantly in terms of individual subject response. This is demonstrated in Fig. 3, which depicts the ratios of change in bone age *vs.* change in chronological age in individual subjects. Similarly, there was no evidence of an

TABLE 3. Subgroup analyses of growth parameters at baseline and 1 and 2 yr on study

	ISS phenotype					LWS phenotype					*P* value: GH ISS *vs.* GH LWS
	Untreated		GH-treated		*P* value	Untreated		GH-treated		*P* value	
	n	Mean ± SE	n	Mean ± SE		n	Mean ± SE	n	Mean ± SE		
Baseline HV (cm/yr)	6	5.2 ± 0.5	9	4.9 ± 0.3	0.666	7	4.8 ± 0.8	8	4.5 ± 0.5	0.714	0.474
Baseline HV SDS	4	−0.8 ± 0.3	9	−1.1 ± 0.4	0.690	5	−1.1 ± 1.2	2	−1.8 ± 0.7	0.735	0.412
Baseline Ht SDS	9	−3.1 ± 0.3	14	−3.3 ± 0.2	0.838	14	−3.1 ± 0.3	12	−3.1 ± 0.3	0.852	0.606
First-year HV (cm/yr)	9	5.2 ± 0.4	14	8.9 ± 0.5	<0.001	14	5.1 ± 0.3	12	8.5 ± 0.4	<0.001	0.443
First-year HV SDS	9	−0.8 ± 0.3	14	3.2 ± 0.4	<0.001	12	−0.7 ± 0.2	10	2.8 ± 0.5	<0.001	0.627
First-year Ht SDS	9	−3.4 ± 0.3	14	−2.5 ± 0.2	0.014	14	−2.9 ± 0.2	12	−2.7 ± 0.3	0.668	0.615
Second-year HV (cm/yr)	9	5.1 ± 0.2	14	7.6 ± 0.3	<0.001	14	5.6 ± 0.4	12	7.0 ± 0.3	<0.013	0.122
Second-year HV SDS	9	−0.6 ± 0.2	14	2.5 ± 0.4	<0.001	12	−0.3 ± 0.2	12	2.1 ± 0.4	<0.001	0.405
Second-year Ht SDS	9	−3.4 ± 0.3	14	−1.8 ± 0.2	<0.001	14	−2.7 ± 0.2	12	−2.4 ± 0.4	0.363	0.189
2-yr Ht gain (cm)	9	10.4 ± 0.5	14	16.6 ± 0.6	<0.001	14	10.6 ± 0.6	12	16.0 ± 0.5	<0.001	0.508

Data are expressed as the mean ± SE. Ht, Height; HV, height velocity.

effect of GH treatment on progression into puberty in subjects with SHOX-D. All subjects were prepubertal at baseline; at 2 yr, six GH-treated subjects with SHOX-D and four untreated control subjects with SHOX-D had entered puberty ($P = 0.731$). Two subjects with TS also spontaneously entered puberty during the 2-yr study period.

Safety

There were no discontinuations due to adverse events in this study. No serious adverse events were reported for subjects with SHOX-D. The three serious adverse events reported in this study occurred in three subjects with TS (scoliosis in two subjects and a fall resulting in a clavicle fracture in a third subject).

At least one treatment-emergent adverse event was reported for 68% of the untreated SHOX-D group, 85% of the treated SHOX-D group, and 96% of the TS group. However, the majority of these events represented common childhood illnesses that would be expected in a pediatric population (such as viral illness, upper respiratory infection, *etc.*). Because clinical trial reports of treatment-emergent adverse events typically garner a high frequency of events apparently unrelated to treatment, this study specifically collected data in a prospective fashion on a number of events that have been previously reported in subjects receiving GH, although not necessarily in a causal manner, as listed in *Subjects and Methods*. These events were reported in small numbers of GH-treated and untreated control subjects with SHOX-D (GH-treated *vs.* untreated control: arthralgia, three of 27 *vs.* two of 25; gynecomastia (males), one of 12 *vs.* zero of 12; increased number of cutaneous nevi, two of 27 *vs.* zero of 25; recurrent otitis media, one of 27 *vs.* one of 25; scoliosis, one of 27 *vs.* zero of 25). No subject in this study developed diabetes.

Laboratory data

IGF-I SDS values at baseline were on average in the low-normal range in each of the study groups, increasing to the upper-normal range during GH treatment but remaining in the low-normal range in the untreated control group (Fig. 4A). IGF-I concentrations exceeded +2 SDS at least once during GH treatment in 10 (37%) subjects with SHOX-D and in nine (35%) subjects with TS; no untreated subject had an IGF-I that exceeded +2 SDS at any visit. IGFBP-3 SDS at baseline were closer to the normal mean than the corresponding IGF-I SDS in all study groups and increased to the upper-normal range in the treated groups (Fig. 4B). As demonstrated in Fig. 4C, there was a strong relationship between IGF-I SDS and IGFBP-3 SDS values during GH treatment, such that no subject had an IGF-I SDS in the upper tertile accompanied by an IGFBP-3 SDS in the lower tertile (the hypothetical risk relationship). No significant changes were noted in thyroid function.

Discussion

This study, the first large-scale, randomized, controlled, multicenter clinical trial of GH treatment in subjects with SHOX-D, demonstrates the efficacy of GH in increasing linear growth in this patient population over a 2-yr study period. Compared with those who received no treatment, the GH-treated group demonstrated a rapid, highly significant increase in height velocity that was evident by 3 months on study. After 1 yr of treatment, the GH group was growing on average 3.5 cm faster than the untreated group. Although the height velocity declined as expected over the second year of treatment, as reported in other conditions (40–43), the GH group nevertheless still had a significantly greater height velocity than the untreated control group at the second-year time point. The increase in height velocity during the 2-yr study period was comparable to the height velocity increase reported in patients with ISS who received similar GH doses (43, 44). The significant increase in height velocity translated into progressive gains in height SDS for the GH-treated group, whose average height SDS almost attained the lower end of the normal range (−2.0 SDS) by the end of the second year. Within the SHOX-D group, treatment response was similar for males and females, for subjects with the ISS phenotype and those with the LWS phenotype. In terms of individual subject responses, 41% of GH-treated subjects with SHOX-D had height within the normal range (above −2.0 SDS) by the end of the second year, whereas only one untreated subject (the tallest subject at study entry) had a normal height at 2 yr. Little information has been published to date regarding GH treatment of patients with SHOX-D, and the data that are available derive from individual case reports or small, nonrandomized series (14, 20, 31). Responses to GH in these reports have varied from negligible to pronounced,

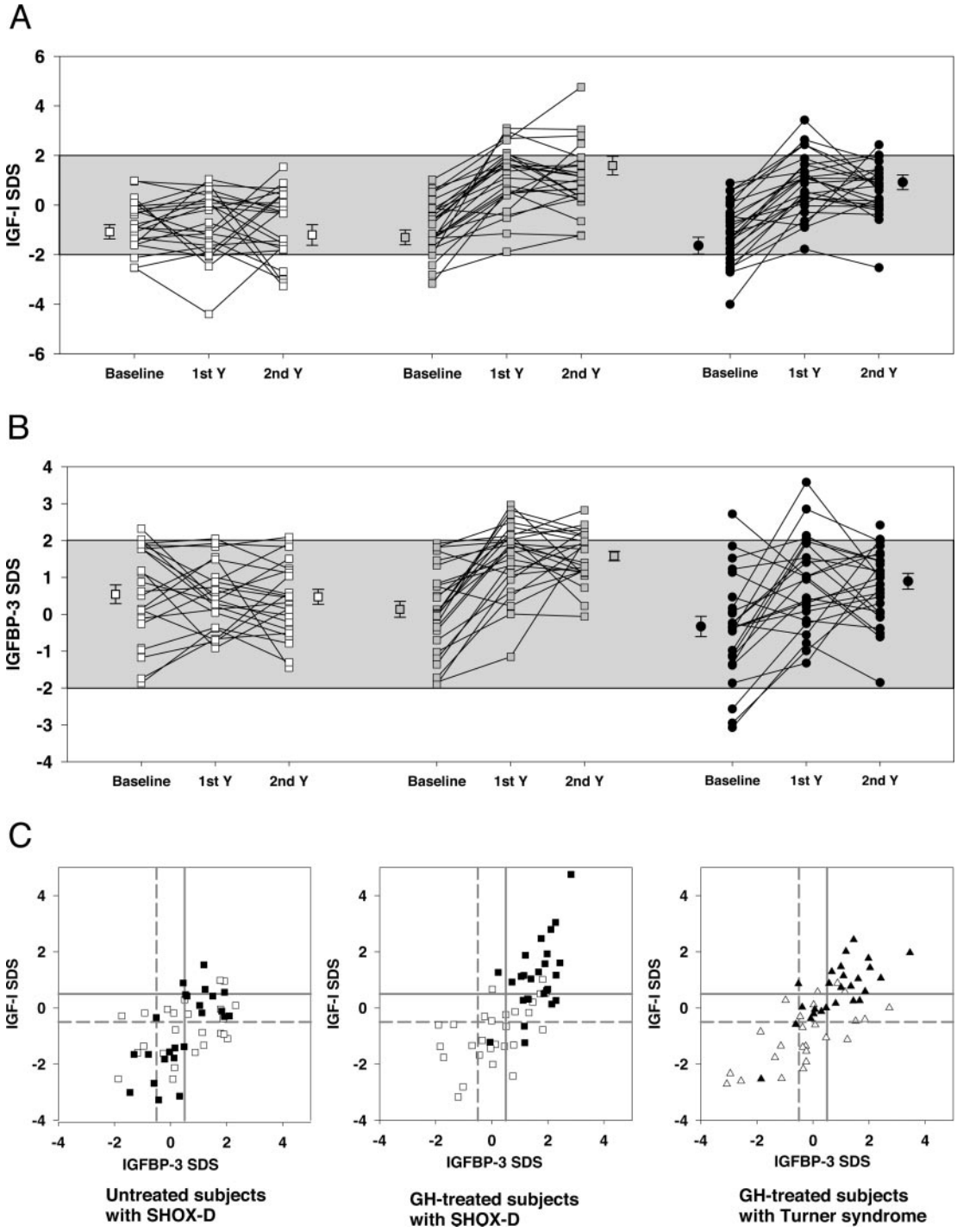

FIG. 3. Individual data for IGF-I SDS (A), IGFBP-3 SDS (B), and the relationship between IGF-I SDS and IGFBP-3 SDS (C) at baseline (□) and 2-yr endpoint (■) in patients with SHOX-D or TS.

providing no clear picture of GH treatment effect. The randomized, controlled study reported here clearly demonstrates a significant GH treatment effect in this patient population.

Because of the similar etiology of the growth disorder in patients with TS and those with SHOX-D, and the well-established efficacy of GH treatment in girls with TS, this study also included a nonrandomized group of subjects with TS to evaluate the comparability of the GH treatment effect across the two different forms of SHOX deficiency. The TS group was somewhat shorter at baseline than the group with SHOX-D, possibly due to additional factors such as aneuploidy or chromosomal imbalance (8, 9); however, the response to GH was very similar between the groups, reflected by the increases in height velocity and height SDS.

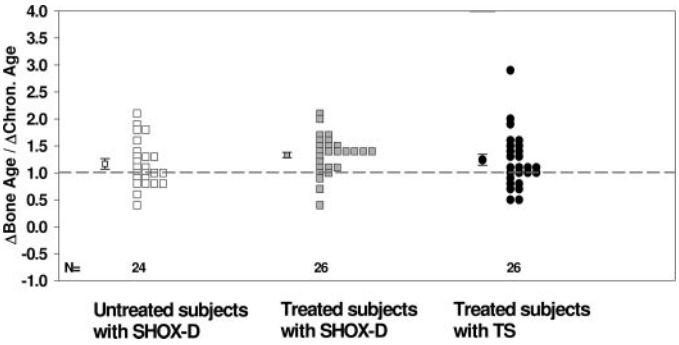

FIG. 4. Group means (± SE) and individual data for the ratio of the change in bone age *vs.* the change in chronological age in GH-treated and untreated groups.

The effect of GH on skeletal maturation in this study was similar among subjects with SHOX-D and those with TS. Bone age was mildly delayed at baseline and caught up somewhat in all treatment groups by the end of the second year. There was a trend toward greater catch-up in both GH-treated groups (SHOX-D and TS) compared with the untreated SHOX-D group, although the difference did not reach statistical significance. The tendency for GH treatment to induce catch-up of skeletal maturation has been observed in other patient populations but has not compromised adult height gain (40, 41, 45, 46). No GH effect was observed with respect to pubertal development, although the subject numbers were small and most of the subjects were still too young at the end of the study for puberty to have begun. The absence of GH effect on the onset or tempo of puberty in long-term studies of subjects with ISS (47) further supports the projection that adult height gains in subjects with SHOX-D will be significant.

There was no evidence of any new or unexpected GH-related adverse events in the SHOX-D patient population. As would be expected because of their higher rates of certain health problems at baseline, the TS group had the highest rate of adverse events. However, the majority of these events represented common childhood illnesses typically seen in pediatric studies or were conditions known to occur with greater frequency in girls with TS, such as edema and otitis media (48). Overall, GH treatment in subjects with SHOX-D appears to have a safety profile comparable to that reported in other pediatric indications for which GH has been previously approved (49, 50).

The mechanism by which SHOX, a homeodomain transcription factor, regulates linear growth and why deficiency of this factor results in short stature is not completely understood. The protein is expressed during pre- and postnatal skeletal development and regulates aspects of chondrocyte differentiation in the growth plate (3–5). Given the relatively low baseline IGF-I concentrations in our subjects, it is tempting to speculate that SHOX may at least in part be involved in regulation of IGF-I gene expression or metabolism. However, IGF-I concentrations responded briskly to GH treatment, the below-average mean baseline value increasing to about 1 SD above the normal mean. This indicates that even if there is an association between SHOX-D and reduced IGF-I, there is no evidence of GH resistance or insensitivity. Although over one third of treated study subjects had at least one IGF-I measurement that fell more than 2 SD above the mean for age and sex, a similar increase occurred in IGFBP-3 concentrations, such that no subject had an elevated IGF-I value in the presence of a low IGFBP-3 concentration, a hypothetical risk profile with respect to neoplasia suggested by a number of epidemiological studies (51–55).

In conclusion, this study confirms that defects in the *SHOX* gene are a fairly frequent cause of short stature and that GH treatment is effective in improving the linear growth of patients with various forms of SHOX-D.

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