

Efficacy and Safety Results of Long-Term Growth Hormone Treatment of Idiopathic Short Stature

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Context: Small clinical trials of GH treatment of idiopathic short stature (ISS) show variable efficacy.

Objective: The study was an analysis of a large GH registry for efficacy and safety of GH treatment of ISS. There was also a comparison with a specific clinical trial.

Design: Up to 7 yr of GH treatment of ISS was evaluated for efficacy and safety in the National Cooperative Growth Study (NCGS).

Setting: The NCGS study was conducted at Genentech, Inc. and included 47,226 patients.

Patients: The ISS group included maximum stimulated GH 10 ng/ml or more and/or a report of ISS by investigator (n = 8018; all included for safety). Cohort 1 (n = 2520) was similar to the clinical trial, cohort 2 (n = 283) included subjects younger than 5 yr of age, and cohort 3 (n = 940) was pubertal at GH start.

Intervention: GH, approximately 0.30 mg/kg-wk, was given.

Main Outcome Measures: These included growth velocities and height SD (HtSDS).

Results: Mean first-year growth velocities in cohorts 1, 2, and 3 increased 4.6, 3.9, and 4.4 cm/yr over pretreatment, respectively. Measures included: baseline mean HtSDS, -2.9, -3.2, and -2.8; mean HtSDS at 1 yr, -2.4, -2.3, and -2.3, respectively. Mean HtSDS after 7 yr in cohorts 1 (n = 303) and 2 (n = 85) and 5 yr in cohort 3 (n = 58) were: -1.2, -1.0, and -1.5, respectively. Cohort 3 shorter treatment time was due to advanced baseline age (mean 13.8 yr) and puberty. Mean HtSDS gain in cohort 1 was comparable with the clinical trial. No new safety signals specific to the NCGS ISS population were observed.

Conclusion: ISS patients in the GH registry demonstrate a significant increase in HtSDS with the safety profile similar to GH-deficient patients. Results were similar to the clinical trial. (*J Clin Endocrinol Metab* 90: 5247–5253, 2005)

GH THERAPY OF children with short stature of unknown etiology or idiopathic short stature (ISS) has demonstrated varying degrees of efficacy in reports over the last decade. Finkelstein *et al.* (1) reported a review of 10 controlled and 28 uncontrolled studies, suggesting that GH therapy tends to increase adult height of children with ISS by about 4–6 cm. Some of the variance reported (1–3) depends on GH dose, age of initiation, duration of therapy, and power of assessment due to the small number of patients involved.

Concerns about the applicability of the data from these trials to children in the clinical practice setting center on both safety and efficacy. We evaluated data from the National Cooperative Growth Study (NCGS, Genentech, Inc., South San Francisco, CA), a large surveillance study of GH use in North American children for the safety and efficacy of GH treatment in ISS. The study data include more than 8000 children assessed for safety and subcohorts of these patients divided by age and pubertal status assessed for efficacy. An

efficacy cohort defined similarly to that in a formal ISS clinical trial (4) allowed for a direct comparison of the NCGS data with that study. Because of its size, the NCGS also provides a unique opportunity to evaluate the safety of growth hormone therapy in patients with idiopathic short stature, especially with respect to rare adverse events.

Patients and Methods

The NCGS is a North American, multicenter, postmarketing surveillance study established in 1985 to follow up the use, safety, and effectiveness of recombinant DNA biosynthetic human GH (somatropin for injection, Nutropin and Nutropin AQ, and somatrem for injection, Protropin, Genentech, Inc.) (5). Data from patients enrolled in the NCGS as of June 30, 2003, were analyzed for this report. At the time of this analysis, the total number of patients enrolled in the NCGS was 47,226, representing more than 160,000 patient-years of exposure to GH.

The pediatric endocrinologists who directed patient care provided anonymous diagnostic and therapeutic data concerning each of the patients enrolled in the NCGS. Inclusion criteria for NCGS were children of either sex treated with a Genentech GH preparation for growth failure who were willing to keep follow-up appointments throughout study participation. Exclusion criteria were patients who were treated with a non-Genentech GH preparation, patients with closed epiphyses, patients with active neoplasms, and patients receiving antitumor therapy for an intracranial lesion within 12 months of enrollment. Approval by the appropriate institutional review board, ethical review committee, or the family for data entry and transmission was the responsibility of each investigator and/or participating institution. Each patient's data were

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Abbreviations: CI, Confidence interval; CRF, case report form; ISS, idiopathic short stature; rh, recombinant human; SDS, SD score; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

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transmitted to the NCGS under a code, the key to which resided with the investigator. The only potential identifier was the patient's date of birth, which was necessary to calculate age.

The NCGS is an observational study; data are not from a controlled, randomized, treatment-blinded clinical trial, nor were diagnostic categories necessarily selected by predetermined criteria. At the baseline visit, defined as the initiation of therapy with recombinant human (rh)GH, and at each patient visit, a case report form was completed and sent to a central location for data entry and analysis. Data entry and management were initially provided by Biometric Research Institute, Inc. (Arlington, VA) and later by Westat, Inc. (Rockville, MD). Data analysis was performed by the Department of Biostatistics, Genentech, Inc.

A patient in the NCGS was designated as having ISS as the primary etiology of his or her short stature by an exclusionary algorithm. Case report forms (CRFs) were reviewed for known etiologies of short stature based on both checkbox and volunteered text information. Review of reported GH stimulation test results provided an additional clinical marker for the ISS designation. Patients were designated as having ISS if their short stature had etiologies such as GH neurosecretory dysfunction, bioinactive GH, and other terms commonly applied to patients with ISS. The ISS etiology was established after other known etiologies of short stature (*e.g.* Turner syndrome, GH deficiency, small for gestational age, Russell-Silver syndrome, organic causes, and chronic renal insufficiency) were ruled out; more than 400 patients were excluded from this analysis because they had a specific diagnosis.

The ISS designation was applied to NCGS patients who met any of the following criteria: 1) maximum stimulated GH of 10 ng/ml or greater and additional confirmatory text reported on the CRF indicating an ISS designation by the patient's physician; 2) maximum stimulated GH of 10 ng/ml or greater and without text or checkbox information reported indicating other known causes of short stature (chromosomal and/or congenital variants, renal disease, organic causes, and isolated GH deficiency); or 3) no GH stimulation test result but text reported on the CRF indicating ISS.

Additional review was made of text reported in follow-up forms that may have affected the etiology determination. Unless clearly related to a pretreatment diagnosis, patients reporting renal disease and development of tumors were left in the ISS diagnosis to prevent censoring of safety data. All patients identified by any of the three ISS criteria listed above were included in the analysis of safety.

For the efficacy analysis presented below, only patients having a stimulation test marker combined with absence of any disconfirming data (items 1 or 2, above) were considered.

Efficacy analyses

For efficacy analyses [growth rate and height SD score (SDS)], further criteria were applied to define three efficacy cohorts. Efficacy cohort 1 included the NCGS patients with baseline characteristics similar to those of patients enrolled in a Genentech-sponsored ISS clinical trial (4) and with at least baseline and yr 1 results. The criteria for cohort 1 were the following: maximum stimulated GH 10 ng/ml or more; no text reported on the CRF contradicting the diagnosis of ISS; baseline chronological age of 5 yr or older; baseline height SDS -2 or less; prepubertal at baseline (Tanner stage 1); naive to previous GH therapy; starting dose of rhGH of 0.25 mg/kg weekly or more.

Patients in efficacy cohort 2 met the same criteria as cohort 1, except that patients in cohort 2 had a baseline chronological age that was younger than 5 yr. Patients in efficacy cohort 3 met the same criteria as cohort 1, except that patients in cohort 3 were pubertal (Tanner stage 2–5) at baseline.

The following data were collected: height, weight, pubertal status, examination of injection sites, GH treatment regimen, chronic concomitant medications, endocrine studies as determined by the patient's physician, patient compliance, and adverse events. Bone age readings were optional but were recorded when available. They were not centrally read and thus could not be used to reliably calculate adult height prediction for this report. Once GH treatment was discontinued, physicians were requested to continue to submit height measurements until the patient had epiphyseal closure and attainment of adult height. Documented adult height data were insufficient for analysis in this report.

Annualized growth rates are expressed as centimeters per year, com-

puted as the change in height (centimeters) divided by the change in age (years). Linear interpolation of heights was used to estimate the height at each year after baseline, using the closest visits before and after each anniversary. Growth rates were computed for each treatment year up to yr 7. In addition, the pretreatment growth rate was computed using the baseline height and the height obtained from the patient's history closest to 12 months before treatment initiation. If there were no prestudy measurements at least 3 months and at most 18 months before treatment initiation, the pretreatment growth rate was set to missing. Thus, the numbers by year for analyses requiring pretreatment growth rate are generally less than the numbers that require only baseline height.

Height SDSs were computed using norms and algorithms from the Center for Disease Control and Prevention (CDC)/National Center for Health Statistics (<http://www.cdc.gov/growthcharts/>) (6) for each treatment year up to yr 7. For any given age and sex, the statistical distribution in the general population of height SDS is normal, with a mean of 0 and an SD of 1. Midparental target heights based on parental heights and patient sex were calculated as described by Tanner (7) and expressed as height SDS using normative data for adults.

For annualized growth rates and height SDSs, separate analyses were performed for patients who completed at least 1 yr, at least 2 yr, *etc.*, up to 7 yr of treatment. For each number of years completed, the annualized growth rates and height SDSs were determined and summarized for each year of treatment up to the number of years in question, using the same patients (an equal n analysis). For cohort 1, further analyses of growth rate data were performed on subcohorts of patients who discontinued treatment early, matched for baseline characteristics with those who continued treatment, as described further in *Results*. All enrollment, treatment, and outcome data are reported as mean \pm SD.

Safety analyses

Adverse event rates were summarized by System Organ Class using MedDRA (a registered trademark of the International Federation of Pharmaceutical Manufacturers Associations) thesaurus terminology (<http://www.meddrasso.com>). Adverse events, serious adverse events, and certain targeted adverse events specified by the protocol (described below) were summarized. Patient exposure to GH was summarized by age group.

Physicians were instructed to report any adverse clinical or laboratory finding when there was a suspicion that treatment with GH may have been related to the adverse event. A suspected association was sufficient to report an adverse event, but it was not necessary to be certain of causality. However, if GH had been unequivocally ruled out as a possible cause, the event did not need to be reported unless it was a targeted event, as defined by the protocol.

Certain targeted adverse events defined by the protocol include the following: cancer, neoplasm (new onset or recurrence), central nervous system tumor, any new-onset or recurring tumor (including leukemia), intracranial hypertension, pancreatitis, new or recurrent slipped capital femoral epiphysis or avascular necrosis, new-onset or progression of scoliosis, arthralgia or arthritis, carpal tunnel syndrome, diabetes mellitus, edema, fracture, gynecomastia, hypoglycemia, hypothyroidism, injection site reaction, or abnormal bone or other growth.

The incidence rates of certain significant adverse events that occurred in the NCGS ISS population were compared with background rates. These included mortality (all causes), new malignancies (all sites), suicides, single seizures, epilepsy (defined as two or more unprovoked seizures), and type 1 diabetes mellitus. The CDC's National Vital Statistics Reports were used to identify annual incidence rates for mortality and suicide by sex and age (5-yr age groups) (8). The National Cancer Institute's Surveillance, Epidemiology, and End Results data (9) were used to identify annual incidence rates for cancers by sex and age (5-yr age groups, with separate rates for ages < 1 yr and 1–4 yr) (available from: http://seer.cancer.gov/csr/1975_200).

Annual incidence rates for epilepsy and single seizures by age (5-yr age groups) were obtained from MacDonald *et al.* (10). Because rates were missing for single seizures in the age groups 10–14 yr and 15–19 yr, a conservative approach was taken in which the lowest value from among the other age groups was assumed for those two age groups. Annual incidence rates for diabetes by age were obtained for type 1 diabetes from the CDC's Diabetes Surveillance Report in 1995 (11) (avail-

TABLE 1. Baseline characteristics

Characteristic	Mean \pm SD			
	Cohort 1 (n = 2520)	Cohort 2 (n = 283)	Cohort 3 (n = 940)	All patients (n = 8018)
Chronological age (yr)	10.5 \pm 2.7	3.7 \pm 0.9	13.8 \pm 1.6	10.9 \pm 3.5 (n = 8018)
Pretreatment growth rate (cm/yr)	4.0 \pm 1.7 (n = 1721)	5.6 \pm 2.3 (n = 198)	4.5 \pm 2.1 (n = 644)	4.4 \pm 2.1 (n = 4751)
Height SDS	-2.9 \pm 0.6	-3.2 \pm 0.8	-2.8 \pm 0.6	-2.7 \pm 0.9
Initial GH dose (mg/kg-wk)	0.31 \pm 0.05	0.32 \pm 0.04	0.31 \pm 0.06	0.30 \pm 0.06
Sex	Number of patients (%)			
Male	1907 (75.7)	191 (67.5)	668 (71.1)	6015 (75.0)
Female	613 (24.3)	92 (32.5)	272 (28.9)	2008 (25.0)

able from: <http://diabetes.niddk.nih.gov/dm/pubs/amerca/contents.htm>).

To determine the expected number of serious adverse events in the NCGS for the background rate analysis, the above incidence rates were multiplied by the actual patient exposure to GH in the NCGS by age and, where rates were presented separately, by sex. The observed incidence in the NCGS was then divided by the expected incidence to obtain a standardized incidence ratio (SIR) or, in the case of mortality, the standardized mortality ratio (SMR). An SIR (or SMR) of 1.0 indicates that the NCGS serious adverse events occurred at exactly the expected rate, given the published background rates and the patient-years of exposure to GH in the NCGS for patients in each age group. Exact 95% confidence intervals (CIs) for SIRs were obtained for each event type, assuming a Poisson distribution for the number of events in the NCGS (12).

Results

Baseline characteristics

The baseline characteristics of all patients with ISS and the three cohorts are shown in Table 1. There were a total of 8018 patients in the NCGS designated as idiopathic short stature, with a total exposure to GH of 24,817 patient-years. Cohort 1, which was selected to match patients in the previously cited Genentech clinical trial, numbered 2520 patients. Cohort 2 (the young cohort) included 283 patients, and cohort 3 (the pubertal cohort) numbered 940 patients. For the efficacy cohorts, mean pretreatment growth rates ranged from 4.0 cm/yr (cohort 1) to 5.6 cm/yr (cohort 2), and mean pretreatment height SDS ranged from -2.8 (cohort 3) to -3.2 (cohort 2). The mean initial rhGH dose was similar for all groups, ranging from 0.30 to 0.32 mg/kg weekly. The sex ratio of approximately 3:1 males to females reflects clinical treatment practices and likely represents a combination of referral bias on the part of referring physicians as well as parental and/or treating physician concern about short stature in males.

TABLE 2. Growth rate (cm/yr) for patients in cohort 1 by number of years treated (mean \pm SD)

Treatment year	Years treated						
	1 (n = 1721)	2 (n = 1446)	3 (n = 1131)	4 (n = 839)	5 (n = 588)	6 (n = 375)	7 (n = 235)
0	4.0 \pm 1.7	4.0 \pm 1.7	4.0 \pm 1.6	4.0 \pm 1.6	4.1 \pm 1.6	4.1 \pm 1.6	4.2 \pm 1.5
1	8.6 \pm 1.8	8.6 \pm 1.7	8.6 \pm 1.7	8.6 \pm 1.7	8.6 \pm 1.6	8.7 \pm 1.6	8.7 \pm 1.6
2		7.5 \pm 1.8	7.5 \pm 1.8	7.4 \pm 1.6	7.2 \pm 1.5	7.1 \pm 1.3	7.1 \pm 1.2
3			7.0 \pm 1.9	7.0 \pm 1.8	6.8 \pm 1.7	6.6 \pm 1.5	6.4 \pm 1.3
4				6.4 \pm 2.0	6.7 \pm 1.8	6.7 \pm 1.6	6.3 \pm 1.4
5					6.1 \pm 2.2	6.6 \pm 1.9	6.5 \pm 1.8
6						5.9 \pm 2.3	6.4 \pm 2.0
7							5.6 \pm 2.3

Efficacy

Table 2 shows annual growth rates for patients in cohort 1 completing 1–7 yr of GH therapy. The greatest number of patients were in the first treatment year, and the number decreases with time. Patients are continually enrolled in NCGS because it is an ongoing study that seeks to capture efficacy and safety data from all children receiving Genentech GH. Thus, at the time of analysis, there were patients who had recently been enrolled, resulting in more patients in the early years. The decrease in the number of patients is also due in part to patients who completed their intended course of therapy and in part to patients who terminated treatment prematurely.

Tables 2 and 3 provide efficacy data for patients completing a given number of years of treatment, accompanied by data in the same subjects for the previous years (equal n's). As seen in the growth rate data in Table 2 and similarly for height SDS data in Table 3, the results for any given year of therapy are similar for patients completing different total years of therapy.

Figure 1 shows the growth rates for the efficacy cohorts 1 and 2, compared with data from the study by Hintz *et al.* (4). Both cohorts demonstrated rapid catch-up growth during the first year of treatment followed by lesser degrees of catch-up in subsequent years, as expected for GH therapy. Patients in cohort 3 had a baseline mean growth velocity of 4.5 \pm 2.1 cm/yr, which increased in yr 1 to 8.9 \pm 2.1 cm/yr and then waned to 7.5 \pm 2.2, 5.8 \pm 2.4, and 4.7 \pm 2.4 cm/yr from yr 2 to 4, respectively. Growth velocity in cohort 3 slowed to 3.2 \pm 2.6 cm/yr in year 5, consistent with advanced puberty and epiphyseal closure. Mean height SDS in cohort 3 was -2.8 \pm 0.6 at baseline and gradually increased to

TABLE 3. Height SDS for patients in cohort 1 by number of years treated (mean \pm SD)

Treatment year	Years treated						
	1 (n = 2520)	2 (n = 2056)	3 (n = 1576)	4 (n = 1138)	5 (n = 775)	6 (n = 487)	7 (n = 303)
0	-2.9 \pm 0.6	-2.9 \pm 0.6	-2.9 \pm 0.6	-2.9 \pm 0.6	-2.9 \pm 0.6	-3.0 \pm 0.6	-3.0 \pm 0.7
1	-2.4 \pm 0.7	-2.4 \pm 0.7	-2.4 \pm 0.7	-2.3 \pm 0.7	-2.3 \pm 0.7	-2.3 \pm 0.7	-2.3 \pm 0.7
2		-2.0 \pm 0.8	-2.0 \pm 0.7	-2.0 \pm 0.7	-2.0 \pm 0.7	-2.0 \pm 0.7	-2.0 \pm 0.7
3			-1.7 \pm 0.8	-1.8 \pm 0.8	-1.8 \pm 0.8	-1.7 \pm 0.8	-1.7 \pm 0.7
4				-1.5 \pm 0.8	-1.5 \pm 0.8	-1.5 \pm 0.8	-1.5 \pm 0.7
5					-1.4 \pm 0.8	-1.4 \pm 0.8	-1.4 \pm 0.8
6						-1.3 \pm 0.8	-1.3 \pm 0.8
7							-1.2 \pm 0.8

-1.5 \pm 0.8 by yr 4. Cohorts 1 and 2 demonstrate similar height SDS gains, with the mean height SDS within the normal range at the final time point for each cohort.

Comparison of the NCGS data in cohort 1 with the clinical trial (4) shows a very similar response in terms of both growth rate (Fig. 1) and height SDS (Fig. 2). Specifically, Fig. 2 demonstrates that mean (\pm SD) height SDS was largely within the normal range by yr 6 and 7. The comparability of the response in NCGS ISS cohort 1 patients and clinical trial ISS patients suggests that the clinical trial outcomes translated into similar efficacy in actual clinical practice.

The possible relationship of growth response to early treatment discontinuation was assessed in a subcohort analysis comparing the growth rates in prepubertal children in cohort 1 under age 11 yr who completed various years of treatment with those who discontinued treatment before the end of the comparable period (Table 4). To ensure that the patients had similar opportunities with respect to duration of treatment,

a suitable enrollment date range was specified for each analysis. The subcohorts who either completed or discontinued treatment in yr 2, respectively, had similar baseline characteristics with respect to age (8.5, 8.4 yr), percent female (24 or 27), pretreatment growth rate (4.2 or 4.5 cm/yr), and baseline height SDS (-3.0, -3.1). The mean first-year growth rate for patients completing at least 2 yr of treatment was 8.6 cm/yr (n = 813), compared with 7.9 cm/yr (n = 100) for those who discontinued treatment in yr 2. Similarly, baseline characteristics were matched for the subcohorts completing or discontinuing in yr 3, and their corresponding growth rates during yr 1 (8.7, 8.1 cm/yr) and yr 2 (7.1, 6.5 cm/yr) were comparable. Finally, baseline characteristics were matched for the subcohorts completing or discontinuing in yr 3, and their corresponding growth rates during yr 1 (8.7, 8.6 cm/yr), yr 2 (7.1, 7.1 cm/yr), and yr 3 (6.7, 6.6 cm/yr) were

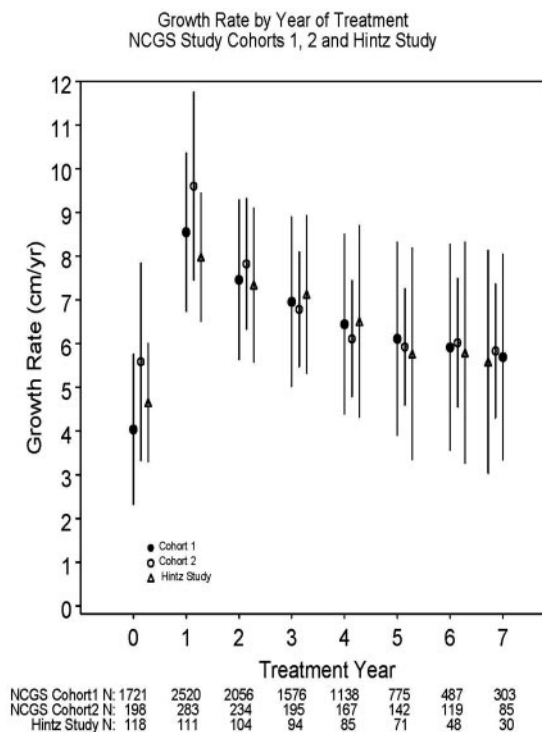


FIG. 1. Growth rate by year of treatment (mean \pm SD) for NCGS cohorts 1 (filled circles), 2 (open circles), and the study by Hintz *et al.* (4) (open triangles).

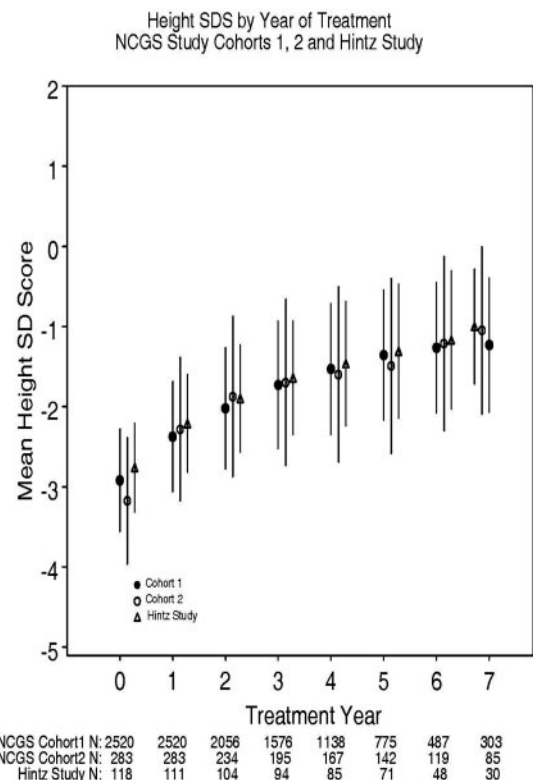


FIG. 2. Height SDS by year of treatment (mean \pm SD) for NCGS cohorts 1 (filled circles), 2 (open circles), and the study by Hintz *et al.* (4) (open triangles).

TABLE 4. Growth rate (cm/yr) for patients in cohort 1 who completed or discontinued treatment during yr 2, 3, or 4 (mean \pm SD)

Year	Completed at least 2 yr (n = 813)	Discontinued during yr 2 (n = 100)	Completed at least 3 yr (n = 678)	Discontinued during yr 3 (n = 102)	Completed at least 4 yr (n = 586)	Discontinued during yr 4 (n = 72)
1	8.6 \pm 1.7	7.9 \pm 1.8	8.7 \pm 1.7	8.1 \pm 1.8	8.7 \pm 1.6	8.6 \pm 1.7
2			7.1 \pm 1.4	6.5 \pm 1.7	7.1 \pm 1.4	7.1 \pm 1.8
3					6.7 \pm 1.6	6.6 \pm 2.0

similar. These data suggest that the likely reasons for discontinuing treatment early were not generally related to growth response.

Because of a concern that some of the patients in these analyses may have had constitutional delay, the three cohorts were analyzed, comparing those with reported bone ages delayed more than 2.5 yr with those whose bone ages were within 2.5 yr of their age. In the case of cohort 1, this yielded a similar number of patients (707 and 743 for yr 1, and 93 and 94 at yr 7) in each group. The growth velocities and height SDS over the 7 yr were very similar for both groups (for yr 1–7 the growth velocity for the group with bone age delay were 8.4, 7.4, 6.9, 6.4, 6.1, 6.3, and 6.1 cm/yr, compared with 8.6, 7.5, 7.0, 6.4, 6.2, 5.6, and 5.4 cm/year for those with no delay). With cohort 2 this same analysis was more difficult, because there were many fewer patients with bone age delay of more than 2.5 yr (3–6 in the group with bone age *vs.* 55–143 in the group without bone age delay). Nonetheless, the growth velocities and the height SDSs were very similar in both groups. Even in cohort 3 (the pubertal cohort), there was no apparent difference in growth velocities and height SDSs between the group with bone age delay and the group without bone age delay for the 4 yr that this cohort could be analyzed. Also, there did not appear to be any difference in cohort 3 in the number of patients available for analysis after yr 4 in the group with bone age delay, compared with the group without bone age delay. In addition, there were no statistically significant relationships in any of the three efficacy cohorts between first-year growth velocity or first-year change in height SDS and age at starting GH therapy, bone age, bone age delay, baseline height SDS at starting GH therapy, sex, or midparental height, except that in cohort 1 the youngest patients had the fastest growth velocities, and in cohort 3 the males had somewhat faster growth velocities than the females.

Safety

In the total NCGS ISS safety cohort of 8018 patients, there were 274 adverse events reported, of which 53 were rated as serious. The serious adverse events included two deaths, one Burkitt lymphoma, and one suicide in a patient with depression. Both were considered unrelated to GH administration by the reporting physician. There were no new safety signals attributed to GH in these 8018 patients.

The incidence of certain significant adverse events was compared with estimated background rates in the general population, as shown in Table 5. These included all causes of death, new malignancies at any site, suicides, single seizures, epilepsy (defined as two or more unprovoked seizures), and type 1 diabetes mellitus. In most categories, the exact 95% CIs

for SIR or SMR included 1.0, indicating that there were no significant differences in risk between the NCGS ISS population and the general population. Overall, the background rate analysis did not reveal a significantly increased incidence of any of the adverse event categories or mortality in the NCGS ISS population as compared with the general population.

Discussion

As previously reported (13), children with ISS make up about 20% of all children entered into the NCGS. We examined the efficacy of GH therapy in patients with ISS, whose data were submitted to the NCGS. Increases in the means for growth rate and height SDS were observed during the first year of treatment, followed by lesser degrees of catch-up over the next 6 yr, as expected. However, even at yr 7, the mean growth rate for cohorts 1 and 2 were greater than the pre-treatment growth rate. In cohort 3, the pubertal cohort, there was a more rapid waning of the growth rate, likely due to pubertal progression, epiphyseal fusion, and completion of growth. When analyzed by height SDS, all three groups increased mean height SDS by approximately 1.5 SD in the first 5 yr. The data demonstrate that GH therapy produced a sustained increase in growth rate in children with ISS for a period of up to at least 7 yr or until there is epiphyseal closure (in cohort 3).

A large database such as the NCGS provides a valid view of clinical practice in a real-world setting, and the large number of patients enrolled tends to compensate for other problems inherent in such databases. When the growth rates of NCGS ISS cohort 1 were compared with those of patients in a clinical trial (4), a remarkably similar growth response was observed. Cohort 1 actually had a slightly better acceleration of growth rate during the first year of therapy, followed by 6 yr of very similar response. The slight difference in the first year may have been due to the large number of patients in the clinical trial who were given their GH as thrice-weekly injections in their first year of treatment rather

TABLE 5. Comparison of adverse event rates with background rates observed and expected numbers of events, SMR or SIR, and 95% CI

Event type	Observed no.	Expected no.	SMR or SIR (95% CI)
Mortality (all cause)	2	9.3	0.2 (0.03 to 0.78)
New malignancies (all sites)	5	3.6	1.4 (0.45 to 3.24)
Suicides	1	0.9	1.1 (0.03 to 5.91)
Single seizures	6	3.1	1.9 (0.71 to 4.20)
Epileptic seizures	1	18.4	0.1 (0.00 to 0.30)
Diabetes	5	4.5	1.1 (0.36 to 2.58)

than daily injections. The majority of patients in cohort 1 initiated treatment with GH divided into six or seven injections per week. A comparison of growth rates between patients who discontinued treatment early with those continuing treatment (matched for baseline characteristics) suggests that poor growth response was not a major reason for early termination of therapy.

The NCGS database did not provide sufficient data on documented adult height for the ISS cohorts. Data from non-treatment studies of ISS and from untreated control groups in treatment studies (2, 3, 14–16) indicate that children with ISS who are not treated with GH typically do not achieve normal adult heights, compared with the general population or midparental target height. The ISS patients in such studies typically achieve mean adult height SDSs between 1.5 and 2.5 SDS below the normal mean.

Several studies have indicated that there is some spontaneous increase in height SDS in untreated patients with ISS, perhaps as much as 0.8 SD; however, children in these studies did not achieve adult heights that were as tall as their target heights (sex-adjusted midparental heights) (17–19). This observation is consistent with the report of Leschek *et al.* (3), in which patients in the control arm of this GH treatment study gained 0.5 SD. A review of GH treatment studies in ISS (1, 2), including a randomized, placebo-controlled study (3), indicates that mean adult heights achieved with standard rhGH treatment regimens typically exceed pretreatment predicted adult heights and may or may not achieve midparental target heights. Height gains of up to 1 SD, or approximately 6 cm, have been achieved, using GH doses of 0.15–0.3 mg/kg weekly and treatment durations ranging from approximately 3 to 7 yr. Additional increases in adult height SDS in ISS have been demonstrated with increased doses up to 0.37 mg/kg-wk (20). Data from the Genentech ISS clinical trial (4) indicated that GH 0.3 mg/kg weekly for an average of approximately 6 yr results in an increase in adult height over pretreatment Bayley-Pinneau-predicted adult height of approximately 5 cm in boys and 6 cm in girls. Considering the similarity of the response of NCGS ISS cohort 1 to the patients in this clinical trial in terms of growth rate and change in height SDS, it appears that GH treatment of ISS in a real-world clinical setting with good clinical management results in similar outcomes.

The response to GH therapy in young patients with ISS (cohort 2, children < 5 yr) was initially better than, and subsequently similar to, that seen in older children in terms of growth rate and change in height SDS, suggesting that substantial catch-up growth can be achieved before entering puberty in children who are evaluated at a young age. The data from cohort 3 indicate that even though pubertal children are limited in the length of time they can respond to GH, they too respond to treatment with significant increases in growth rate and height SDS.

Data in the NCGS are periodically and continually examined for safety signals (21, 22). When the NCGS subset of patients with ISS was examined for this report, no new safety signals emerged. The overall pattern of adverse events was consistent with those reported in clinical trials of GH in ISS as well as with more than 18 yr of GH postmarketing experience. Furthermore, when the incidence of certain signifi-

cant adverse events that were seen rarely in the NCGS ISS population were compared with those in the general population, there did not appear to be any increased incidence of these adverse events in the population of children with ISS who were treated with GH.

In conclusion, this analysis of NCGS data demonstrates that long-term GH therapy is safe and effective in children with idiopathic short stature and that the outcomes in the real-world clinical setting can be expected to be comparable with that reported in formal clinical trials. Use of GH in non-GH-deficient children raises the question of which children should be treated. This issue has recently been reviewed by Allen and Fost (23).

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