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Insulin Growth Factor-Based Dosing of Growth Hormone Therapy in Children: A Randomized, Controlled Study

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Context: Weight-based dosing of GH is the standard of care for short children, although IGF-I is thought to be the main mediator of GH actions on growth.

Objective: The objective of the study was to test whether IGF-I levels achieved during GH therapy are determinants of the growth responses to GH treatment.

Design: This was a 2-yr, open-label, randomized, IGF-I concentration-controlled trial. Prepubertal short children [n = 172, mean age 7.53 yr, mean height SD score (HT-SDS) −2.64] with low IGF-I levels (mean IGF-I SDS −3.56) were randomized to receive one of two GH dose-titration arms in which GH dosage was titrated to achieve an IGF-I SDS at the mean [$IGF_{(low)}$ group, n = 70] or the upper limit of the normal range [+2 SDS, $IGF_{(high)}$ group, n = 68] or to a comparison group of conventional GH dose of 40 μg/kg/d (n = 34).

Setting: The study was conducted in a multicenter, outpatient setting.

Primary Outcome Measure: Change in HT-SDS over 2 yr was measured.

Results: One hundred forty-seven patients completed the trial. Target IGF-I levels were achieved in the dose-titration arms within 6–9 months. The changes in HT-SDS were +1.0, +1.1, and +1.6 for conventional, $IGF_{(low)}$, and $IGF_{(high)}$, respectively, with $IGF_{(high)}$ showing significantly greater linear growth response ($P < 0.001$, compared with the other two groups). The $IGF_{(high)}$ arm required higher doses (>2.5 times) than the $IGF_{(low)}$ arm, and these GH doses were highly variable (20–346 μg/kg/d). Multivariate analyses suggested that the rise in the IGF-I SDS significantly impacted height outcome along with the GH dose and the pretreatment peak-stimulated GH level.

Conclusion: IGF-I-based GH dosing is clinically feasible and allows maintaining serum IGF-I concentrations within the desired target range. Titrating the GH dose to achieve higher IGF-I targets results in improved growth responses, although at higher average GH doses. **(*J Clin Endocrinol Metab* 92: 2480–2486, 2007)**

RECOMBINANT HUMAN GH (rhGH) is widely used for the treatment of short stature resulting from GH deficiency (GHD) or insufficiency (1, 2) as well as other growth disorders (3). However, GH dosing is empirical in the range of 25–100 μg/kg/d and is based on weight (4–10). Although a dose-response relationship has been demonstrated, there is a large variability in response (4, 5, 8, 10).

IGF-I is the main mediator of GH actions on linear growth (11–14). Dependency of serum IGF-I concentrations on GH dose has been shown in controlled clinical studies (5, 15, 16) and correlates with the increase in height SD score (SDS) (5). We therefore hypothesized that titration of GH doses to achieve a prespecified IGF-I target should allow the dosage of rhGH to be individualized, based on the GH needs and sensitivity of each patient, and would lead to growth responses that are related to the target IGF-I level.

GH treatment has an excellent safety profile, but uncommon side effects such as benign intracranial hypertension, slipped capital femoral epiphysis (SCFE), and worsening of scoliosis require monitoring during treatment. Whereas no dose-response relationship has been observed between these adverse events and GH dose, it is conceivable that there may be a relationship between the amount of GH, or the attained concentration of IGF-I, and side effects. Even though it was shown in some epidemiological studies that the incidence of certain malignancies is higher in individuals whose serum IGF-I concentrations is at the upper quartile *vs.* the lowest quartile (17–19), there is currently no evidence of a higher risk for the development of cancer in patients treated with GH (20–22). It is of note, however, that one study suggested a possible increase in the frequency of colon cancer and Hodgkin lymphoma in former GH recipients (23), and another study suggested a possible increase in the frequency of second malignancies in children with GHD and a history of preexisting tumors (24). Because IGF-I levels above the normal range may pose a potential risk to patients, it is recommended that IGF-I levels be regularly monitored and maintained within the normal range (20).

Thus, IGF-I levels during GH treatment are relevant to both safety and efficacy. We therefore tested an IGF-based approach for GH dosing. The goal of this strategy is to bring the low IGF-I levels frequently found in short children into

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Abbreviations: Δ, Change; GHD, GH deficiency; HbA_{1c}, hemoglobin A_{1c}; HT-SDS, height SDS; IGFBP, IGF binding protein; LOCF, last observation carried forward; rhGH, recombinant human GH; SCFE, slipped capital femoral epiphysis.

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preselected age- and gender-appropriate levels and maintain them within this predefined range. Such a strategy should take into consideration variation in GH sensitivity, reflect the specific GH requirement of a patient, and allow individualization of GH treatment in children.

Patients and Methods

This clinical trial (37 sites in the United States) was approved by the institutional review board in all centers and was conducted in accordance with the Declaration of Helsinki (25). Written informed consent was provided by a parent/legal guardian before any study-related activities.

Study design

This was a 2-yr, open-label, randomized, IGF-I concentration-controlled trial (a design that randomizes subjects to achieve a specified pharmacodynamic response). The primary objective of this study was to test the null hypothesis that in short, IGF-deficient children, two treatment groups having unequal changes in IGF-I induced by GH would have no difference in height increase over 2 yr of GH therapy. The study was designed to compare treatment outcomes with rhGH in children suspected of GHD, who had rhGH dose adjusted regularly, to achieve an IGF-I SDS of either −0.5 to +0.5 [$IGF_{(low)}$ group, n = 70] or +1.5 to +2.5 [$IGF_{(high)}$ group, n = 68]. A group receiving a conventional GH dose of 40 μg/kg/d (n = 34) was included for comparison. Patients were randomized in a 2:2:1 ratio to the three treatment groups.

Therapy with rhGH (Norditropin delivered by NordiPen using NordiPenMate; Novo Nordisk A/S, Bagsvaerd, Denmark) was initiated at 40 μg/kg/d in all treatment groups. For the IGF-I target groups, GH doses were titrated using a prespecified algorithm: a 20% dose change was used for each SD unit between actual and target IGF-I. GH doses were adjusted beginning at the month 1 visit and at each subsequent three-monthly visit until end of study. In the conventional-therapy group, doses were maintained at 40 μg/kg/d. In the two IGF-I level-targeted groups, dose changes were calculated based on the difference between measured and target IGF-I SDS, which was 0 for the $IGF_{(low)}$ group and +2 for the $IGF_{(high)}$ group.

Patient population

Subjects were required to have a height SDS (HT-SDS) less than −2, serum IGF-I SDS −1.0 or less, a bone age 9 yr or younger for boys or 7 yr or younger for girls, and to not have entered puberty (using a criteria of Tanner I breasts for girls and testicular volume less than 3 ml for boys by Prader orchidometer) within 3 months of visit 1 (26, 27). Twelve children were enrolled with a taller height than the inclusion criteria. The most common reason was that they were reported in the screening visit to be less than −2 SDS for height but at the baseline visit were found to have heights greater than −2 SDS. Because they had already signed consent forms and been entered into the study, they have been included in the data analysis. A subanalysis excluding these children was performed and the results were indistinguishable. Because our analysis was an intention-to-treat approach, we included all enrolled patients. Pubic hair development, up to and including Tanner stage 2, was permitted at study entry. GH testing was not used as an inclusion criteria. Exclusion criteria included prior use of rhGH, previous GH stimulation testing, or growth retardation attributable to other causes, *e.g.* diabetes, metabolic or bone disease, chromosomal disorder or syndrome, intrauterine growth retardation, *etc.* Withdrawal criteria included omission of greater than 10% of scheduled rhGH doses in two 3-month intervals, failure to obtain two or more serum IGF-I tests at 3-monthly intervals, or chronic use of glucocorticoids.

Clinical and laboratory assessment

Data collection included concomitant illness and medications, physical examination, funduscopy, standing height (in quadruplicate measured using a wall-mounted stadiometer), weight, determination of IGF-I, pubertal staging, checks for scoliosis and SCFE, x-ray determination of bone age [left hand-wrist radiograph according to Greulich and Pyle (28)] centrally read by a single blinded observer, blood sampling [for thyroid functions, clinical biochemistry, fasting glucose, insulin, and hemoglobin A_{1c} (HbA_{1c})], and urinalysis. All safety laboratory tests, except for IGF-I, were performed centrally (MRLI, Highland Heights, KY). A standardized GH stimulation test (arginine/levo-Dopa) was used to determine pretreatment GH status and allow a *post hoc* analysis of potential effect of GH status on treatment outcomes.

Serum IGF-I (DSL-5600), IGF binding protein (IGFBP)-3 (DSL-6600), and GH (DSL-1900 double monoclonal immunoradiometric assay) assays were performed at Diagnostic Systems Laboratories (Webster, TX). The IGF-I SDS calculations were provided by Diagnostic Systems Laboratories.

Study visits occurred at months 0 (randomization), 1, 3, 6, 9, 12, 15, 18, 21, and 24 (end of study). Assessments of adverse events, height, weight, IGF-I, funduscopy, and vital signs were conducted at all of these visits. Physical examination for scoliosis and SCFE occurred at all visits. The month 12 and month 24 visits included all laboratory evaluations performed at screening. A complete physical examination was conducted every 6 months, with brief examinations at other visits. X-ray assessment of bone age was obtained at baseline and repeated at the final visit.

Statistical analysis

The primary analysis of the prespecified null hypothesis was conducted on the intent-to-treat population, which included all randomized patients who received study medication and who had at least one post-baseline height and IGF-I assessment. Analysis of covariance was used to test for treatment effect with baseline HT-SDS as a covariate on change from baseline of HT-SDS for each visit. Last observation carried forward (LOCF) was used to impute missing values for the intent-to-treat population. Allowing for a 10% noncompleter rate, the sample size was selected to allow for 80% power to detect a difference of 0.4 in HT-SDS between the two groups with a combined SD of 0.6 at an alpha level of 0.05. A third group, receiving conventional weight-based dosing, was added strictly for comparison. The primary end point for the study was the change in HT-SDS. The investigators and study personnel remained blinded to the aggregate changes in the primary end point until the randomization code was broken at study end. All reported *P* values are two sided and not adjusted for multiple testing.

Results

Demographics, baseline information, and study completion data

The demographic variables and baseline measures of enrolled patients are summarized in Table 1. At the time of enrollment, mean age was 7.53 ± 2.40 yr, mean HT-SDS was −2.64 ± 0.61, mean IGF-I SDS was −3.56 ± 1.74, and mean bone age was 5.51 ± 1.93 yr (2 yr behind chronological age). All patients were prepubertal. The treatment groups did not differ significantly in age, gender, ethnicity, height, IGF-I levels, peak GH, or bone age. A total of 172 subjects [70, 68, and 34; in the $IGF_{(low)}$, $IGF_{(high)}$, and conventional groups, respectively] were enrolled, 171 were exposed to study medication, and 86% or 147 patients completed the study. The mean duration of treatment for all enrolled patients was 22.4 months (median 24 months, range 3–25 months). Approximately half the patients had a peak stimulated GH greater than 10 ng/ml.

Primary efficacy analysis

HT-SDS, IGF-I SDS, and GH dose. Mean values of the change (Δ) in HT-SDS (ΔHT-SDS) during the course of the study are presented in Fig. 1A. All three treatment arms showed increases in HT-SDS during the course of the study. The null hypothesis was rejected ($P < 0.001$). The $IGF_{(high)}$ group had

TABLE 1. Baseline demographics

		$IGF_{(low)}$	$IGF_{(high)}$	Conventional	All
Subjects randomized (n)		70	68	34	172
Subjects exposed (n)		70	67	34	171
Subjects completed (n)		62	55	30	147
Age (yr)	Mean (SD)	7.40 (2.48)	7.52 (2.29)	7.82 (2.48)	7.53 (2.40)
	Min-Max	(2.9, 13.1)	(3.8, 13.5)	(3.2, 12.6)	(2.9, 13.5)
Sex (M/F)		54/16	53/15	25/9	132/40
HT-SDS	n	70	67	34	171
	Mean (SD)	−2.66 (0.73)	−2.67 (0.56)	−2.51 (0.42)	−2.64 (0.61)
	Min-Max	(−5.1, −1.3)	(−4.3, −1.5)	(−3.5, −1.8)	(−5.1, −1.3)
IGF-I, SDS	n	57	54	29	140
	Mean (SD)	−3.75 (2.08)	−3.57 (1.47)	−3.17 (1.44)	−3.56 (1.74)
	Min-Max	(−9.5, 2.5)	(−6.4, −0.8)	(−5.7, 0.3)	(−9.5, 2.5)
GH stimulation test (ng/ml)	n	68	63	34	165
	Mean (SD)	8.93 (6.27)	9.65 (5.26)	10.24 (6.12)	9.47 (5.86)
	Min-Max	(0.1, 36.1)	(0.2, 21.5)	(2.8, 26.9)	(0.1, 36.1)
	<7 ng/ml	29	22	12	63
	≥7 ng/ml	39	41	22	102

Min, Minimum; Max, maximum; M, males; F, females.

the greatest increase in HT-SDS among the three groups (1.58 SDS) at the end of the study (LOCF), which was statistically larger than the other two groups that achieved HT-SDS increases of 1.08 and 1.00 [for the $IGF_{(low)}$ and conventional groups, respectively, $P < 0.001$ for both]. The $IGF_{(low)}$ and conventional groups did not significantly differ from each other at any time point. Annualized growth velocities achieved by the $IGF_{(low)}$, $IGF_{(high)}$, and conventional groups were 9.71, 11.20, and 9.01 cm/yr at 12 months and were 8.38, 10.03, and 8.16 cm/yr at 24 months, respectively.

IGF-I SDS values of the three treatment groups during the course of the study are presented in Fig. 1B. Mean IGF-I SDS showed a rapid increase in all three groups during the first month after initiation of GH treatment. Target IGF-I values were generally reached within 6–9 months with the prespecified dosing algorithm. The $IGF_{(high)}$ group had a target IGF-I SDS value of 2.0 (1.5–2.5): as a group, this target was reached at 9 months, and these IGF-I SDS values were maintained throughout the study. The $IGF_{(low)}$ group had a target IGF-I SDS value of 0 (−0.5 to 0.5), and this target was reached by 6 months and was then maintained. IGF-I SDS values for the conventional group were not titrated, and the mean IGF-I SDS level achieved in this group at end of study (LOCF) was 0.97. The IGF-I SDS values for the $IGF_{(high)}$ group were significantly higher than for the $IGF_{(low)}$ and conventional therapy groups from 6 months onward ($P < 0.001$), and there were no differences between the mean IGF-I SDS for $IGF_{(low)}$ and conventional groups. IGFBP-3 levels also rose in response to GH therapy, reaching levels around 0.5 SDS in all three groups; however, unlike the IGF-I data, there was no significant separation between the IGFBP-3 or IGFBP-3 SDS levels among the three treatment groups (data not shown).

GH dose requirements

The mean daily doses of GH for the three treatment groups were 110 (median 98, range 20–346) μg/kg/d for the $IGF_{(high)}$ group, 33 (median 28, range 9–114) μg/kg/d for the $IGF_{(low)}$ group, and 41 (median 41, range 34–45) μg/kg/d for the weight-based GH dosing comparison group (Fig. 1C). By independent *t* testing, the $IGF_{(high)}$ group received a substantially larger mean GH dose than the other two groups ($P < 0.001$), but there were no significant differences in the mean dose between the $IGF_{(low)}$ group and the comparison group ($P = 0.423$). Dose distributions in the $IGF_{(low)}$ and $IGF_{(high)}$ groups are presented in Fig. 2 and demonstrated a dramatic variability in GH sensitivity in these patients.

Correlation between change in HT-SDS and change in IGF-I SDS or cumulative dose

The changes in HT-SDS from baseline for all the patients were plotted against the changes in IGF-I SDS from baseline to LOCF (Fig. 3). A significant correlation was observed between these two variables (correlation coefficient r = 0.50, $P < 0.001$). Similarly, the changes in HT-SDS from baseline were plotted against the cumulative GH dose that each patient received during the study, and the correlation coefficient was observed to be 0.43 ($P < 0.001$). These results indicate that the change in HT-SDS from baseline is positively correlated with both the IGF-I SDS change from baseline and with the cumulative GH dose.

Multivariate analysis of height outcome

In addition to the correlation analysis described above, multivariate analyses were performed to identify prognostic factors at baseline that had significant impact on change of HT-SDS at the end of the 2-yr treatment period. The initial baseline prognostic factors we included in the model were treatment group, sex, age, body mass index, HT-SDS, peak GH level, IGF-I SDS, and IGFBP-3. The following three factors were identified (and their contribution to the model): height outcome was related to the treatment group (42%), inversely to the baseline peak GH level (39%), and inversely to the baseline IGF-I SDS (15%).

Because other researchers have evaluated the impact of some postbaseline factors (29–31), we also added the following postbaseline factors into the model: changes from baseline to 24 months in IGF-I SDS and IGFBP-3 as well as the cumulative GH dose. Whereas ΔIGFBP-3 was not significant, the treatment group and baseline IGF-I SDS also

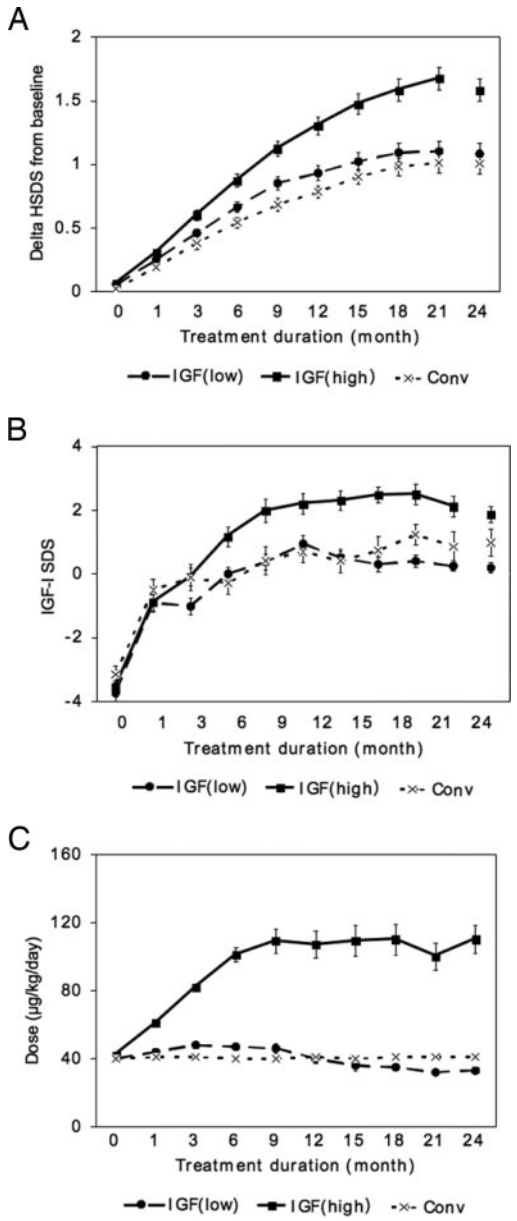

FIG. 1. HT-SDS, IGF-I SDS, and GH dose over time. A, HT-SDS change from baseline. B, IGF-I SDS values over time. C, GH dose over time. Values are mean ± SE.

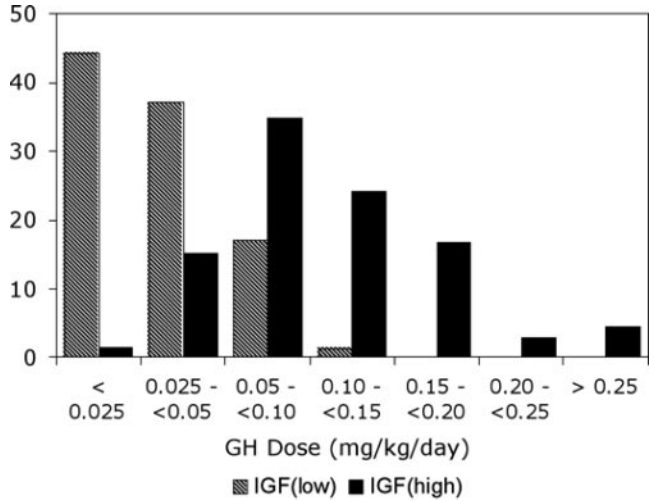

FIG. 2. Histogram of GH dose by treatment groups at the end of the study. Dose distribution in $IGF_{(low)}$ group (n = 70) and $IGF_{(high)}$ group (n = 66). *Vertical bars* represent the percentage of patients in each GH dose range at the end of the study (LOCF). The variability of GH sensitivities is evident, particularly in the $IGF_{(high)}$ group.

became nonsignificant. The final model included only three variables: baseline peak GH level (30%), ΔIGF-I SDS (30%), and cumulative dose (34%).

Safety assessments

Over the 2 yr of study, reported adverse events occurred in 95.7% of patients in the $IGF_{(low)}$ group, 86.6% of patients in the $IGF_{(high)}$ group, and 82.4% in the conventional treatment group. The treatment-emergent adverse event profiles were similar for the three treatment groups. The most commonly reported treatment-emergent adverse events were upper respiratory tract infection, headache, fever, coughing, and injection site hematomas. There was no occurrence of intracranial hypertension or malignancy during the study. There was one case of SCFE reported in the $IGF_{(high)}$ group and 11 cases of worsening scoliosis (three in the conventional, four in the $IGF_{(low)}$ group, and four in the $IGF_{(high)}$ group). Only two patients withdrew from the study due to adverse events, which were eye pain and injection site inflammation (both in the $IGF_{(high)}$ group).

Using blinded, centralized readings, bone age was delayed by approximately 2 yr in all three groups at baseline (Table 2). The bone age to chronological age ratios were 0.71–0.74 at baseline. The bone age to chronological age ratios were 0.84–0.85 for the three groups at 24 months. After 2 yr of GH treatment, bone age showed an increase of 2.45–2.82 yr, and no differences were identified among the three groups. Although, on average, skeletal maturation exceeded corresponding changes in chronological age, the increase in bone age did not detract from the overall benefit that resulted from increases in height SDS. There were no differences in either the baseline or 24-month bone ages between males and females or the degree of advancement of the bone age over the 24-month treatment period among the treatment groups when separated by gender. Although the change in fasting serum insulin levels from baseline in the $IGF_{(high)}$ group was greater than that of the $IGF_{(low)}$ and conventional treatment groups, mean serum insulin remained within the normal range for all groups. In addition, fasting serum glucose levels and HbA_{1c} levels remained normal and did not differ among the three groups (Table 2). Eight patients (four males and four females) entered puberty by the end of the study. There were no differences among the three treatment groups in terms of the Tanner staging at 2 yr.

Discussion

The dosage of GH for treatment of children has historically been based on body weight. However, dramatic variability in response is frequently observed, reflecting differences in the severity of the GHD and the sensitivity to GH treatment. Higher GH doses achieve greater increases in height but with

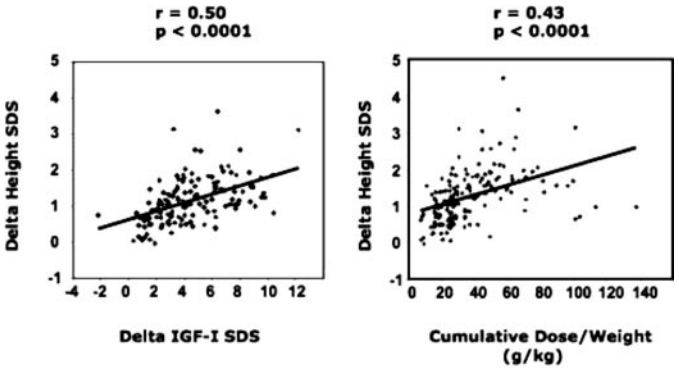

FIG. 3. Relationship between GH-induced IGF-I levels or cumulative GH dose and HT-SDS change from baseline. Correlation between ΔHT-SDS and ΔIGF-I SDS is presented in the *left panel* (combined three groups). Correlation between ΔHT-SDS and cumulative GH dose (grams per kilogram) is presented in the *right panel*. LOCF method was used. Combined n = 170.

wide variability of both the growth response and the accompanying IGF-I increase (5). IGF-I has been identified as the major mediator of GH-induced somatic growth. A dosing algorithm based on IGF-I response might therefore better reflect the true GH requirement of a patient and allow individualization of GH treatment. This approach has not previously been attempted and represents a potential clinical tool for management of GH treatment. In patients with adult GHD, GH dose titration is commonly used to avoid side effects; a recent study by Hoffman *et al.* (32) demonstrated that randomizing patients to a fixed dose of GH or a dose titration approach that maintained IGF levels within the (broad) range of normal, and increasing the dose up to the tolerated dose, leads to similar efficacy but fewer reported side effects in patients receiving the individualized treatment regimen. That study, however, did not attempt to achieve specific IGF-I targets such as those used in our study and was unable to show superior efficacy of the IGF-based dose-titration approach.

The $IGF_{(high)}$ group, titrated to the upper portion of the normal range, demonstrated significantly greater height gains than the $IGF_{(low)}$ and conventional groups with a height increase from a mean of −2.67 HT-SDS to −1.09 HT-SDS and was approximately 0.5 SDS greater than in the other two groups. Such growth benefit, if expressed in standing height, means that patients in the $IGF_{(high)}$ group gained approximately 3 cm more in height than the comparison groups after 24 months of treatment with GH. Whether additional gains would result from longer treatment periods with this protocol, or whether the 24-month response might represent a period of rapid catch-up growth that has long-term benefits, is unknown. However, the lack of difference in the advancement of bone age in the group titrated to a higher IGF-I would appear to indicate that this height gain is likely to be translated into an increased adult height.

The randomized, concentration-controlled design used in this study reveals the broad range of doses required to achieve specific serum IGF-I targets. This range indicates a wide range of sensitivity to GH in the children enrolled. Moreover, the finding of variable responses in growth rates at a specific IGF-I target indicates heterogeneity of response to serum IGF-I exposures. The explanations for these ranges of sensitivity at a molecular level can only be realized with further study but may involve variations in both GH and IGF signaling pathways (33, 34). The pretreatment secretagogue-stimulated GH level was inversely related to the growth response. It may be the case that some non-GHD patients harbor a degree of GH insensitivity, possibly due to mild genetic changes in the GH signaling pathways as has been previously suggested (35–39). Because this reduced growth in non-GHD occurs in the face of similar IGF-I levels, it suggests that these patients also harbor a degree of IGF insensitivity or some other non-GH-IGF-related problem with growth.

Interestingly, the response of serum IGFBP-3 levels to GH was not different among the three groups.

By a multivariate analysis, higher IGF-target assignments, low stimulated GH, and low baseline-IGF-I SDS were independent predictors of greater treatment responses, demonstrating proof of concept for IGF-I-based dosing as well as the prognostic significance of the severity of the GH secretion abnormality. A second multivariate analysis, including parameters collected during treatment, also indicated that the response to GH depends inversely on peak GH to a greater degree than previously suspected (38). In addition, the rise in the IGF-I SDS was directly (and independently) related to

TABLE 2. Safety assessment during treatment

		$IGF_{(low)}$	$IGF_{(high)}$	Conventional	Overall *P* value
Bone age (yr)	Baseline	5.6 (2.08)	5.5 (1.82)	5.4 (1.9)	
	EOS	7.9 (2.28)	7.9 (2.11)	8.2 (2.05)	
	Change from baseline	2.5 (1.12)	2.7 (0.99)	2.8 (0.95)	0.4
Insulin (μU/ml)	Baseline	9.12 (5.46)	9.61 (5.00)	10.81 (7.20)	
	EOS	7.77 (9.20)	12.24 (8.04)	10.33 (6.92)	
	Change from baseline	−1.63 (10.34)	4.13 (8.60)	−1.11 (11.39)	0.05
FSG (mg/dl)	Baseline	85.9 (12.37)	87.3 (15.41)	91.7 (20.42)	
	EOS	85.2 (6.27)	85.2 (11.12)	87.8 (9.58)	
	Change from baseline	−2.0 (12.23)	−1.8 (19.23)	−5.5 (21.55)	0.5
HbA_{1c} (%)	Baseline	5.04 (0.33)	5.00 (0.33)	5.10 (0.32)	
	EOS	5.20 (0.31)	5.23 (0.33)	5.24 (0.32)	
	Change from baseline	0.15 (0.22)	0.22 (0.31)	0.18 (0.17)	0.4
Body weight (kg)	Baseline	18.8 (5.22)	18.6 (4.45)	19.9 (6.16)	
	EOS	26.6 (7.90)	28.3 (6.09)	27.6 (9.69)	
	Change from baseline	7.7 (3.58)	9.8 (3.01)	7.9 (3.94)	

Data are presented as mean (SD). FSG, Fasting serum glucose; EOS, end of study.

the growth response achieved, supporting the study hypothesis. Additionally, the cumulative GH dose itself, independent of impact on IGF levels, was directly (and independently) related to growth response. This correlation of GH dose and response suggests that at least some of the growth-promoting effects of GH may be independent of the measurable rise in serum IGF-I. This result is compatible with the mouse model of combined IGF-I and GH receptor knockouts, which demonstrated that the loss of GH action resulted in a potent further reduction in growth on top of that achieved by eliminating IGF-I alone (37).

The apparent safety of the higher GH dose in the $IGF_{(high)}$ group did not differ from that of the other two groups, with an incidence of adverse events that was similar to that observed in other studies. However, maintaining IGF-I levels within the normal range by adjusting GH dose might diminish the potential risks of excessive IGF-I levels during GH therapy, including the theoretical increase in long-term cancer risk. Notably, in fixed dose trials, 20–50% of the patients sustain IGF-I levels above the upper limit of normal (5, 10). Our study was not powered to detect the safety of IGF-based dosing in terms of rare side effects, and certainly no information is available regarding the long-term safety of such a regimen, especially in terms of cancer risk.

The increased risk of cancer reported among normal individuals with IGF-I levels at the upper quartile, compared with those with the lowest quartile, raises concerns about the implications of raising serum IGF-I to high levels for a prolonged period of time. In this study, we have shown that a dosing strategy that raises IGF-I to the upper limit of normal is associated with higher growth rates and higher GH doses. Our study was designed not to establish that this dosing strategy should be clinically implemented but rather to demonstrate the feasibility of IGF-based GH dose titration and the importance of monitoring the IGF-I levels achieved on therapy. In fact, concerns about safety, *vis a vis* cancer, may lead clinicians to titrate the serum IGF-I to a lower target, based on the clinical scenario and other concerns, such as an IGF-I target below the mean for patients who are survivors of malignancies or those with other high-risk conditions.

Our study has a number of limitations, which should be considered. First, we compared only two IGF-I targets and the possibility that intermediate growth would also have been seen at a midway IGF-I target (*e.g.* +1 SD) cannot be excluded. Second, it is impossible to conclude with this 2-yr trial that the dosing strategy used will lead to increased adult height (although this possibility exists, given the similar bone ages in the three groups).

In conclusion, we have shown here that IGF-based GH dosing is clinically feasible, leads to the attainment of desired preselected IGF-I levels and allows maintaining serum IGF-I concentrations within the desired target and avoids IGF-I levels substantially outside the normal range. Titrating the GH dose to achieve higher IGF-I targets results in higher growth responses, generally at higher GH doses. The wide range in GH doses required to achieve specific IGF-I targets illustrates the variability in GH sensitivity found among pediatric patients with short stature and provides rationale for the concept of individualization of GH dosing. The long-term growth outcome and safety of IGF-based dosing regimens remain to be determined.

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