Height Velocity Targets from the National Cooperative Growth Study for First-Year Growth Hormone Responses in Short Children

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Context: Although GH has been used to treat short stature in GH deficiency (GHD) and other conditions for more than 40 yr, criteria for satisfactorily defining targets for GH responsiveness have never been developed.

Objective: The objective of this study was to present the first-year growth expressed as height velocity (HV) for prepubertal boys and girls with idiopathic GHD, organic GHD, idiopathic short stature, or Turner syndrome from Genentech's National Cooperative Growth Study to derive age-specific targets for GH responsiveness for each etiology and gender.

Design and Population: Using data from the National Cooperative Growth Study, we constructed curves of response to GH during the first year of treatment with standard daily doses in naive-to-treatment prepubertal children with idiopathic GHD (2323 males, 842 females), organic GHD (582 males, 387 females), idiopathic short stature (1392 males, 465 females), or Turner syndrome (1367 females).

Main Outcome Measure: For each category, mean pretreatment and mean ± 1 and ± 2 SD for the first-year HV on GH were assessed. Mean and mean $\pm$ 1 SD for HV were plotted *vs.* age at baseline (initiation of GH treatment) and compared with mean pretreatment HV.

Results: HV plots for each category as a factor of age at baseline are presented. Mean $-$ 2 SD HV plots approximated the pretreatment HV.

Conclusion: Using baseline age- and gender-specific targets will assist clinicians in assessing a patient's first-year growth response. We propose that HV below the mean $-$ 1 SD on these plots be considered a "poor" response. These curves may be used to identify patients who may benefit from GH dose adjustment, to assess compliance issues, or to challenge the original diagnosis. **(*J Clin Endocrinol Metab* 93: 352–357, 2008)**

Growth failure is difficult to define. Although there are a number of systems for the classification of growth disorders, they are problematic because diagnostic categories have not always been clearly defined and frequently overlap (1).

A clear definition of growth response after intervention with therapies such as GH is also lacking. Although GH has been used for treating short stature in GH deficiency (GHD) and other conditions for more than 40 yr, criteria for defining satisfactory GH response targets have never been developed. The range of GH response is large; differences can be attributed to diagnosis, age, GH dose, parental height (Ht), compliance, intercurrent illness, other (endocrine) therapies, and still poorly defined molecular and biochemical factors that may include the structure and concentration of GH receptors, the robustness of the

0021-972X//$15.00/0

Printed in U.S.A.

doi: 10.1210/jc.2007-1581 Received July 17, 2007. Accepted November 5, 2007.

First Published Online November 13, 2007

Abbreviations: GHD, GH deficiency; hGH, human GH; Ht, height; HV, height velocity; IGHD, idiopathic GH deficiency; ISS, idiopathic short stature; NCGS, National Cooperative Growth Study; OGHD, organic GH deficiency; TS, Turner syndrome.

postreceptor signaling cascade, IGF-I transcriptional and translational efficiency, and epiphyseal responsiveness to GH, IGF-I, and other factors.

Several attempts have been made to define and predict growth response. More than 20 yr ago, Frasier *et al.* (2) published a dose-response curve for human GH (hGH) based on observed responses. Dose responsiveness has also been looked at in more recent studies using higher GH dosages (3–5). In addition to dose-response models and reports, various prediction models were developed (6–8). Of these, the models described by Ranke *et al.* based on data from the Kabi International Growth Study registry are best known. Ranke's first mathematical model predicted the growth response of prepubertal children with idiopathic GHD (IGHD) to exogenous recombinant hGH (7). Other prediction models for different etiologies, such as Turner syndrome (TS) and small for gestational age followed, suggesting that the models would help identify the factors determining the observed variability of GH sensitivity (9, 10). Such models of predicting the growth response to hGH do not completely account for the variability observed in GH responsiveness; mostly, they predict around 50% and, at best, 70% of the variability (9), and clearly evidence-based criteria for better defining GH responsiveness are needed. To develop such evidence-based reference data and to aid clinicians in evaluating GH responsiveness, we used data from the Genentech National Cooperative Growth Study (NCGS) to construct plots of growth response during the first year of treatment with standard daily GH doses in prepubertal children, aged 2–14 yr at onset of GH treatment. Target growth responses for the purposes of this paper were defined as height velocity (HV) in the first year of GH treatment; change in Ht SD score (SDS) and HV SDS in the first year of GH treatment were also examined to assess the relative merits of their use *vs.* HV as the target.

The NCGS was initiated in 1985 after the withdrawal of pituitary-derived GH because of Creutzfeldt-Jakob disease and in response to a request by the Food and Drug Administration to monitor the efficacy and safety of recombinant hGH. Since that time, the NCGS registry has grown to become the largest and longest-standing repository of GH-related data in North America, containing demographic and outcomes data from more than 54,000 children with growth-related disorders and encompassing more than 180,000 patient years of experience (11). The NCGS provides an opportunity to evaluate the treatment trends over time across several childhood growth disorders.

Here, we use growth data for the first year of GH treatment from 4297 prepubertal boys and 3061 girls with IGHD, organic GHD (OGHD), idiopathic short stature (ISS), or TS to develop age-, sex-, and diagnosis-specific growth targets of responsiveness.

Patients and Methods

Using data from the NCGS, we studied first-year growth response to GH in four common growth disorders. The first-year HV was determined using the time point at which follow-up Ht was measured that was closest to 1 yr after the initiation of GH therapy provided that the time point was within 90 d of 1 yr. The HV was computed as an annualized HV (centimeters per year). Dose was computed as the average dose during the time over which the HV was computed. We selected previously untreated subjects with Ht SDS less than −2 at onset of GH treatment and with ages between 2 and 14 yr at onset of GH treatment. Baseline is defined as the age at initiation of GH treatment with a daily or six times weekly injection schedule. Patients were prepubertal at the end of the first year of GH treatment, *i.e.* boys with testes volume more than 3 ml, girls with Tanner breast stage of at least 2, and patients with Tanner pubic hair stage of at least 2 were excluded. If the testes volume for a boy at least 13 yr old was unknown or if the breast stage for a girl at least 11 yr old was unknown, the patient was excluded from analysis. From among these subjects, we further selected subjects who had been identified by the NCGS investigators as having IGHD, OGHD, ISS, or TS.

This research was conducted in accordance with the guidelines in The Declaration of Helsinki and was formally approved by the appropriate institutional review committees or its equivalent. This approval and informed consent were obtained from all subjects.

For each gender and etiology, mean pretreatment and mean ± 1 SD for first-year HV on GH were plotted against subject age at onset of GH treatment. Like all the data, the pretreatment HV data are cross-sectional. A smooth curve was fitted as a function of baseline age through the HVs of individual subjects using nonparametric loess regression (12), which generates a smooth curve defining the mean response at each age. The PROC LOESS procedure in SAS (SAS Institute, Cary, NC) was used to perform these analyses.

The absolute values of the residuals from this first fit were computed. Next, these residuals were fit *vs.* age, again using SAS loess. Last, the SD was taken as the square root of $\pi/2$ times this second fit (using the relationship between the mean of a half-normal distribution with the SD of the corresponding normal distribution).

Ht SDS were computed using the method of Kuczmarski *et al.* (13) from the US Centers for Disease Control 2000 growth charts, and HV SD scores were computed using data from Tanner *et al.* (14). The same statistical curve-fitting methodology was used to obtain the curves for the change in Ht and HV SDS.

Results

Sample sizes for fitting curves were as shown in Table 1. The 10th, 50th, and 90th percentiles for dose during the first year are

TABLE 1. Sample sizes for fitting curves

	Females			Males		
Etiology (age in yr)	**2–6**	**6–10**	**10–14**	**2–6**	**6–10**	**10–14**
IGHD	117	537	188	249	1367	702
OGHD	83	223	78	104	343	130
ISS	40	291	134	87	810	491
TS	118	878	371	NA	NA	NA

NA, Not applicable.

TABLE 2. Dose (mg/kg·wk)

Etiology (yr)	Females			Males		
	10th percentile	50th percentile	90th percentile	10th percentile	50th percentile	90th percentile
IGHD	0.25	0.30	0.35	0.25	0.30	0.35
OGHD	0.19	0.29	0.35	0.18	0.30	0.35
ISS	0.27	0.30	0.36	0.27	0.30	0.35
TS	0.28	0.35	0.38	NA	NA	NA

NA, Not applicable.

shown in Table 2. Doses were generally close to 0.30 mg/kg·wk, except for TS, in which 0.35 mg/kg·wk was typical.

The results for this investigation are primarily graphical and are presented in Figs. 1–5. These display the relationship between raw data and fitted curve (see Fig. 1), fitted curves, SDs, and pretreatment HV (see Fig. 2), fitted HV curves (means ± 1 SD) for each etiology and gender (see Fig. 3A–G); and examples of change in Ht SDS (see Fig. 4) and HV SDS (see Fig. 5) as alternative ways of expressing growth response for comparison.

As an example of the fitting procedure, Fig. 1 displays the raw data with fitted curves for naive to GH, prepubertal boys with IGHD. Curves for HV means ± 1 SD are depicted over the range of baseline ages. We decided to present the means ± 1 SD in all curves rather than means ± 2 SD, because the mean − 2 SD curve was found to correspond closely to the pretreatment HV and thus represents very limited improvement in HV. Figure 2 illustrates this phenomenon in naive, prepubertal boys with IGHD.

Figure 3 shows the mean ± 1 SD HV during the first year of GH therapy, as well as the pretreatment mean HV for females and males with IGHD (Fig. 3, A and B), OGHD (Fig. 3, C and D), ISS (Fig. 3, E and F), and females with TS (Fig. 3G). The first-year mean HV was higher at younger ages. The SD of the HV varied only somewhat with age at baseline, with more variability for females than males.

Using the same male IGHD patients as in Fig. 2, Fig. 4 shows the same mean and mean ± 1 SD curves for change in Ht SDS, and Fig. 5 does the same for HV SDS. Compared with the HV, there is greater variation in means and SDs with respect to baseline age, especially for the HV SDS.

Discussion

Clinical experience shows there is considerable variability in response to therapy with GH in children with short stature, at least with a standard weight-based dosing schedule (15, 16). We still do not completely understand why children with GHD, for whom therapy is directed at replacing absent GH, should exhibit such a wide range in response, which persists even when we take into account such variables as statural deficiency before therapy, bone age, midparental Ht, and duration of treatment (17). For children with IGHD, variability in growth response reflects, at least in part, the well-documented inaccuracies inherent in the diagnosis. For children with OGHD, variability in response certainly reflects the impact of radiotherapy, chemotherapy, and chronic illness. In TS, variability of response is commonly observed and inadequately understood and could reflect differences in the degree of target tissue SHOX (short stature homeobox) deficiency inherent in a heterozygous genetic condition (18). Finally, with ISS, it is commonly accepted that this diagnosis encompasses a heterogeneous group of disorders, and a spectrum of responses to GH therapy should not be surprising. Recognition of the wide range of clinical responsiveness to GH should serve to challenge the traditional, weight-based GH dosing that has been in use for more than 40 yr (19). The evidence-based criteria we present here take the next step in helping to define growth responses to GH in several childhood disorders.

First-year responses to GH in four different groups of patients were derived from the very large postmarketing surveillance database NCGS. The first point to note, as seen in Fig. 2 for IGHD males, is that the mean pretreatment HV curve approximates the

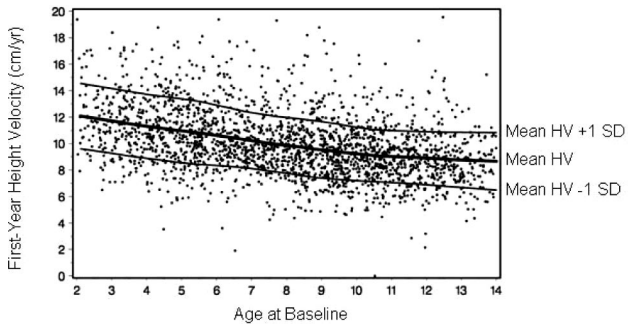

FIG. 1. Points represent first-year growth responses to daily GH expressed as HV at age of treatment onset (x-axis) in naive, prepubertal IGHD males.

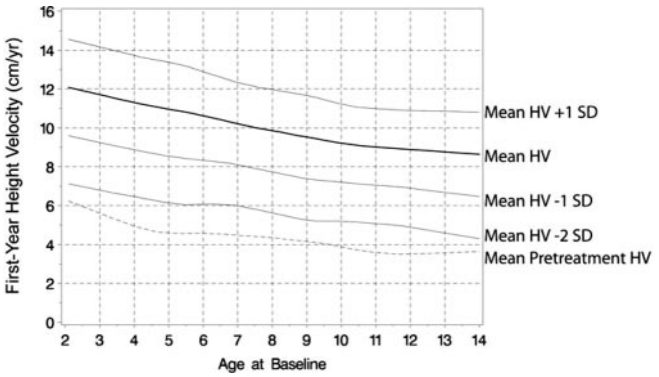

FIG. 2. First-year growth responses to daily GH expressed as HV at age of treatment onset (x-axis) in naive, prepubertal IGHD males. Data given for mean and mean ± 1 and − 2 SD.

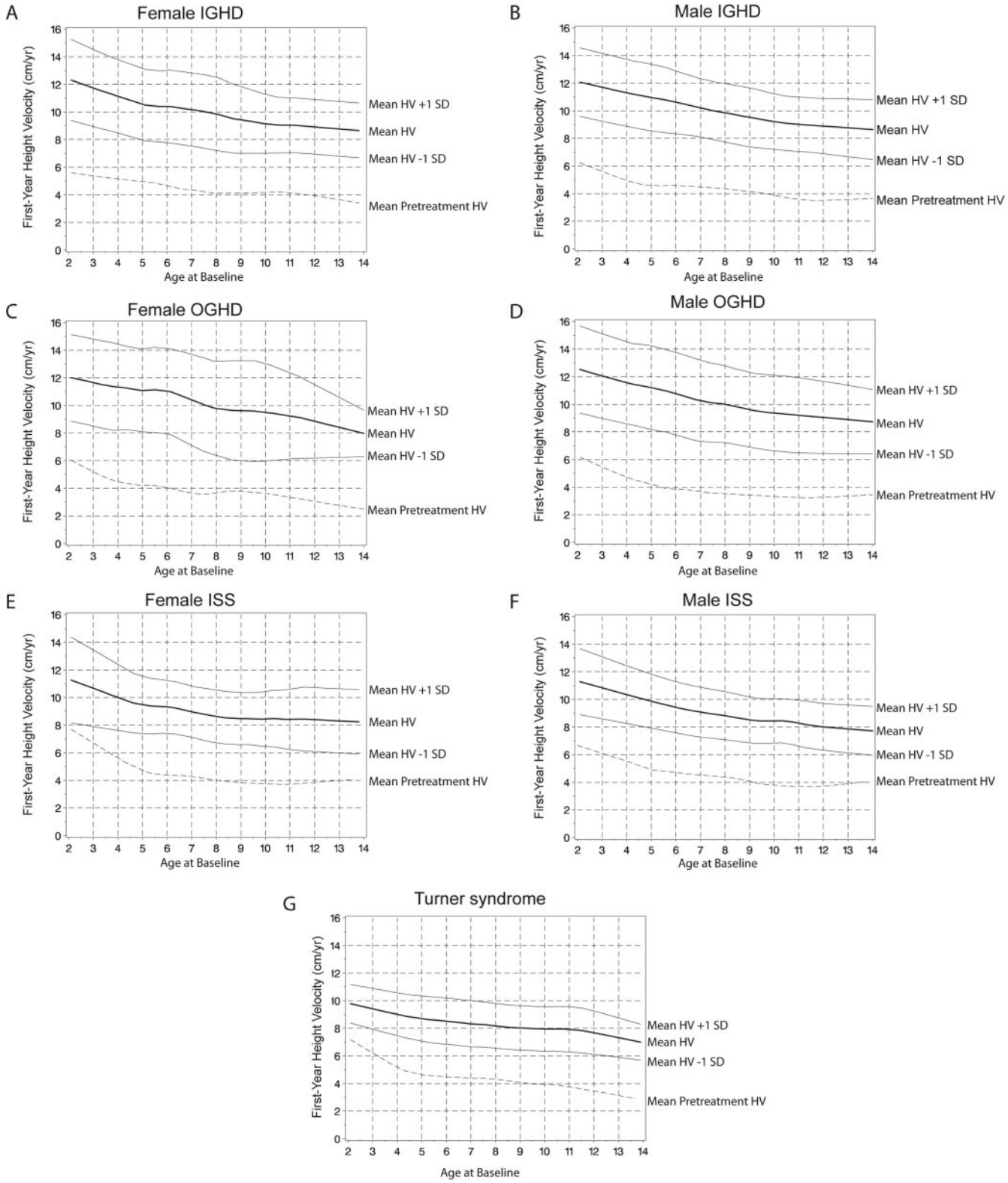

FIG. 3. First-year growth responses to daily GH expressed as HV at age of treatment onset (x-axis) in naive, prepubertal females and males with IGHD (A, B), OGHD (C, D), and ISS (E, F), and females with TS (G). Data given for mean and mean ± 1 SD.

curve for the first-year mean − 2 SD for HV for all of the conditions evaluated. This indicates that children with HV at the mean − 2 SD during the first year of GH therapy are not exhibiting the expected improvement in growth velocity. If this is observed, it prompts a number of questions, such as the correctness of the diagnosis, compliance issues, *etc.* We will address these issues toward the end of *Discussion*.

As seen in Fig. 3, mean HV varies similarly across etiologies

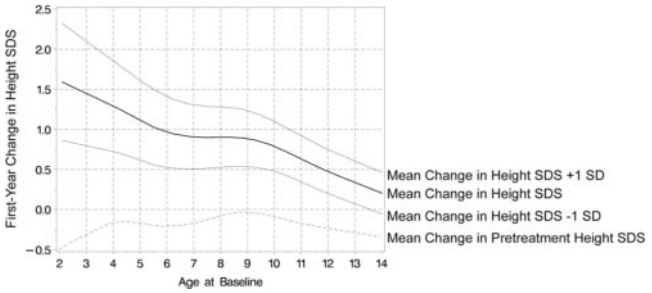

FIG. 4. First-year growth responses to daily GH expressed as change in Ht SDS at age of treatment onset (x-axis) in naive, prepubertal IGHD males.

with age at baseline. Hence, HV needs to be interpreted in the context of age at baseline (as well as of etiology of growth failure and gender). The similarity of patterns across etiologies as well as HVs over the baseline age range emphasizes the importance of age at initiation of treatment.

As seen in Fig. 4, the mean and SD of the change in Ht SDS both differ substantially with age. Hence, the interpretation of the change in Ht SDS during the first year of treatment, as shown, and subsequently (data not shown) is highly dependent on age (as well as etiology and gender). Interpretation of the pretreatment change in Ht SDS in males with IGHD is also highly dependent on age, as shown in Fig. 4 by the dashed curve for the mean annualized change in Ht SDS before treatment began. Generally, these children were decreasing in Ht SDS before treatment, but the rate of decrease varied substantially with age. Similar results are seen for females and for other etiologies of short stature. Thus, a 1-yr increase in Ht SDS of 0.5 may be acceptable in patients greater than 10 yr of age but would be considered poor in younger children. The larger mean and SD at younger ages is the result of the fact that the SD of Ht is smaller at younger ages. For example, an increase in Ht during the first treatment year of 10 cm at a young age results in a larger change in Ht SDS than the same 10 cm at an older age. This observation on change in Ht SDS has to be taken into consideration when one compares two cohorts in which the age at onset of GH treatment differs considerably.

As seen in Fig. 5, HV SDS depends even more on age at baseline than the change in Ht SDS. Hence, the need is even greater for interpreting the change in HV in a child during treatment in the context of the general experience of children of the same etiology, age, and gender. The major problem with HV SDS as a primary efficacy endpoint is that it does not take into consideration the disturbances in the timing of puberty that are often seen in the etiologies discussed in this article.

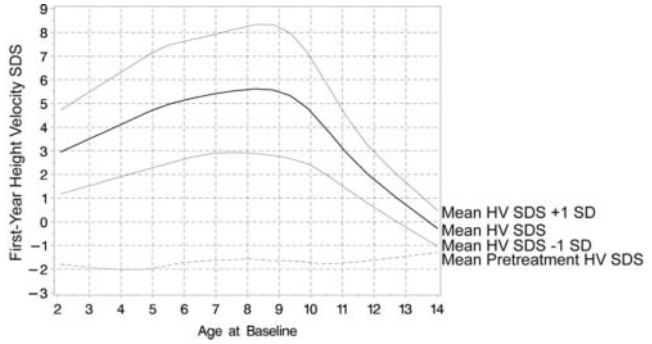

FIG. 5. First-year growth responses to daily GH expressed as HV SDS at age of treatment onset (x-axis) in naive, prepubertal IGHD males.

These first-year GH-treatment HV curves (as well as the curves for change in Ht SDS and HV SDS) should be viewed as conservative for a number of reasons.

For example, there is an unknown amount of noncompliance in all groups. There are also diagnostic challenges such as distinguishing between some forms of IGHD (when GHD is isolated and not part of idiopathic multiple pituitary hormone deficiency) and ISS that make the IGHD group more heterogeneous. These issues could inflate the SDs for each of the response endpoints and lower the means for the IGHD group. Thus, the computed mean − 1 SD and mean − 2 SD curves could be lower than what the curves would be without these problems, especially for IGHD. Hence, if a child's on-treatment first year HV is below the on-treatment mean − 1 SD curve, then effort should be made to explore possible causes of poor response to GH treatment. As mentioned previously, we suggest using the mean − 1 SD instead of, for example, the mean − 2 SD because, in all cases (as can be observed in Fig. 2), the mean − 2 SD is very close to the pretreatment HV curve and would hardly be considered an improvement.

These curves can serve as a practical tool for clinicians to use when comparing the first-year HV of specific patients to the HV of a large population in the NCGS database. If the HV in the first year of treatment is considered "substandard," as defined here, one should reconsider whether 1) the diagnosis is correct, 2) there is comorbidity, such as undiagnosed underlying illness, 3) compliance is adequate, or 4) undetermined factors are affecting the clinical response to GH, such as defects of GH and/or IGF sensitivity. Results for HV are notably more homogeneous with age than change in Ht SDS or HV SDS. Based on the analyses presented, we suggest that the clinician use HV as the primary efficacy endpoint for evaluating treatment for short stature based on age at baseline, gender, and etiology.

In summary, the use of age at baseline-, gender-, and etiology-specific first-year growth response curves offer the clinician a benchmark against which to assess the progress of an individual patient and can contribute to evidence-based decision making to maximize the efficacy of GH treatment.

Acknowledgments

We thank Joan Jacobs for the critical reading of this manuscript and her contributions to the discussion. Genentech, Inc., provided writing assistance for this manuscript.

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Disclosure Statement: B.B. and B.L. are employees of Genentech and hold stock with Genentech. J.F. received consulting fees from Genentech, Tercica, Fibrogen, DiObex, Theravance, and Acumen Sciences. H.A. and R.G.R. received consulting fees from Genentech.

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