Effect of Growth Hormone Therapy on Height in Children With Idiopathic Short Stature

A Meta-analysis

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Context: Use of growth hormone (GH) therapy to promote growth in children with idiopathic short stature is controversial. A fundamental issue underlying the controversy is uncertainty about the magnitude of effectiveness of GH for this condition.

Objective: To determine the effect of GH on short- and long-term growth in idiopathic short stature.

Study Design: Systematic review of controlled and uncontrolled studies.

Data Sources: MEDLINE (1985-2000), key journals, cross-referencing of bibliographies, abstract booklets, and experts.

Study Selection and Data Extraction: We performed a meta-analysis of all studies satisfying the inclusion criteria for idiopathic short stature: initial height below the 10th percentile, normal stimulated GH levels (>10 µg/L), absence of comorbid conditions, no previous GH therapy, treatment with biosynthetic GH, and inclusion of major outcome measures.

Primary Outcome Measures: Growth velocity and height SD score (number of SDs from mean height for age and sex) at baseline and after 1 year to evaluate the short-term effect of GH. Adult height was analyzed to evaluate the long-term effect of GH.

Data Synthesis: Ten controlled trials (434 patients) and 28 uncontrolled trials (655 patients) met the inclusion criteria. While baseline growth velocities were equivalent at baseline, 1-year growth velocity of the GH-treated group significantly exceeded that of controls by 2.86 cm/y. Similarly, in uncontrolled trials, growth velocity increased after 1 year, and height SD score increased from −2.72 at baseline to −2.19. In controlled studies, the adult height of the GH-treated group significantly exceeded controls by 0.84 SD, and in uncontrolled trials the adult height attained after GH treatment (−1.62 SDs) exceeded that predicted at baseline (−2.18 SDs). These results suggest an average gain in adult height of approximately 4 to 6 cm (range, 2.3-8.7 cm) with GH therapy. Given current treatment costs, this corresponds to more than $35000 per inch (2.54 cm) gained in adult height in idiopathic short stature.

Conclusions: Treatment with GH results in short-term increases in growth for children with idiopathic short stature, and long-term GH can increase adult height. These results are fundamental to decisions about GH use and raise questions about the goals of treatment. Use of GH for idiopathic short stature in clinical practice will depend on its efficacy in promoting growth and the value of this effect to families, physicians, and third-party payers.


The use of biosynthetic growth hormone (GH) to treat children with idiopathic, familial, or constitutional short stature (hereafter referred to as idiopathic short stature) is controversial. There is ongoing debate among the medical community, third-party payers, and families of affected children about the appropriateness and effectiveness of treatment. More than 1 million children in the United States are potential candidates for GH treatment and are thus affected by decisions about GH use. Corresponding annual expenditures for GH potentially range from $196 million to $18 billion, depending on the criteria for treatment. Although historically reserved and approved by the Food and Drug Administration for treatment of short stature in children with classic GH deficiency, Turner syndrome, renal failure, or Prader-Willi syndrome, GH therapy has been suggested for many other conditions (including idiopathic short stature) and the literature suggests that its use in such children is expanding. Children with idiopathic short stature constitute the largest population of potential pediatric candidates for GH. For this
A computerized literature search using MEDLINE was conducted to identify all published articles from 1985 to 2000 on treatment of children with biosynthetic GH. (Biosynthetic GH became widely available and supplanted pituitary GH for patients in 1985, the first year in which it was approved by the Food and Drug Administration for children lacking adequate endogenous GH.) The search terms used were (growth hormone or somatotropin or somatropin or somatrem) + (therapy or treatment) + (growth or height) + (child or adolescent), limited to the English language. In addition, manual searches of 4 journals (JAMA, the Journal of the American Medical Association, The Journal of Pediatrics, Pediatrics, and Acta Paediatrica) from 1996 to 2000 were conducted, and meeting abstract books in these journals were reviewed as well as those of the Lawson Wilkins Pediatric Endocrine Society and the Endocrine Society. Bibliographic references from all retrieved articles also were reviewed. Pharmaceutical companies were contacted. To ensure complete collection of data and to avoid inadvertent exclusion of negative results, external experts reviewed the list of eligible studies.

STUDY SELECTION

Two reviewers (B.S.F. and U.M.) screened all citation abstracts obtained from the literature and manual searches (n = 1823) to determine whether each study met basic criteria for further in-depth review (ie, primary studies of GH use in children). For all abstracts meeting these basic criteria (n = 761), the published article was retrieved for further review.

Three reviewers then conducted detailed assessments of each article to identify all those appropriate for inclusion in the systematic review. The reviewers independently assessed descriptive information about each study using a standardized abstraction form, then met to review each study’s appropriateness for inclusion. Before discussion, there was 92% agreement regarding study inclusion and exclusion, and after discussion, there was 100% agreement. Articles were included if (1) the topic was short stature (height below the 10th percentile for age); (2) the children presented as GH-naive patients (ie, no previous GH treatment) and had an absence of classic GH deficiency (peak GH levels ≥10 pg/L on ≥1 standard stimulation tests); (3) there was an absence of comorbid conditions that impair growth (such as Turner syndrome, renal failure, intrauterine growth retardation, and GH insensitivity) or, as in 2 studies, if raw data were available to enable reanalyses without such patients; (4) the treatment was biosynthetic (not pituitary-derived) GH in the range of 0.14 to 0.40 mg/kg per week for a minimum of 6 months (studies using pituitary-derived GH may not be directly applicable to current treatment regimens because biosynthetic GH has been available only since 1985, and questions about equivalence in potency and dosing would limit interpretation of results); (5) the study contained at least 5 patients; (6) patients did not have previous treatment with sex steroids or anabolic agents potentially affecting growth; (7) the last outcome data for analysis were obtained on a minimum of 50% of the original subjects; and (8) the study presented primary data and included appropriate height outcome measures (growth velocity [in centimeters or inches per unit time] or height [SD score; height Z score]). Of the 761 studies reviewed, 53 qualified for inclusion. More than 90% of excluded studies either included comorbid conditions or lacked primary data.

DATA ABSTRACTION

Abstraction of primary data was performed independently by 3 reviewers using a standardized form. Data abstracted were sample size, mean age, sex distribution, study design (controlled or uncontrolled trial), baseline pubertal status, growth variables (ie, height, growth velocity, and predicted adult height), and growth outcome measures (height, growth velocity, and adult height [defined in the articles reason, together with controversy about the distinction between disorder and the bounds of natural variation, idiopathic short stature represents a major threshold in the expansion of nontraditional use of GH. Despite several studies, the effectiveness of GH in increasing growth for children with idiopathic short stature is not clear. Interpretation of the literature has been hampered by studies involving small numbers of participants, variation in outcome measures (eg, short term vs long term and height vs growth velocity), differing treatment effects reported, and absence of structured synthesis of data. In addition, ethical and practical issues, such as long-term daily injections of placebo to children, have made randomized controlled trials of GH challenging.

The lack of clear data on effectiveness of GH therapy in idiopathic short stature is particularly important. Differing perceptions of GH effectiveness result in marked variation among physicians about recommending GH therapy, and there are striking inconsistencies among third-party payer policies for coverage of GH. This variation, together with the controversies surrounding GH use, the vast number of children affected by decisions about GH, and the high cost of treatment, underscores the importance of quantifying the short- and long-term effects of biosynthetic GH therapy on growth in idiopathic short stature. Previous reviews have primarily been narrative, without structured synthesis and quantitative combination of results. Recent articles call for such outcome data, including structured synthesis of the existing literature, to provide clearer guidance on GH use and to form the foundation for dialogue among physicians, families, and policy makers. The goal of this study, therefore, was to perform a systematic review of the contemporary literature on GH treatment of idiopathic short stature in children to quantify the effects of GH on short- and long-term growth.

RESULTS

Ten controlled trials (reported in 19 separate articles) and 28 uncontrolled trials (reported in 34 separate articles) met the inclusion criteria for meta-analysis of GH treatment of idiopathic short stature.
as advanced bone age (>16 years in boys and >14 years in girls) and/or slowing of growth rate (0.5-2.0 cm/y)). Height was expressed as the mean height SD score (ie, number of SDs from the mean height for age and sex). The Tanner-Whitehouse or the Bayley-Pinneau method was used to predict adult height in all articles reporting this growth variable. For 5 studies in which data were stratified by covariates that were not of primary importance to the analysis (eg, age or sex), we combined strata weighted by sample size. Authors were contacted to clarify questions about published and unpublished data. The 3 reviewers discussed each article to reach consensus on abstracted data. If a series of related articles was published from a single trial or study group (as occurred in 6 trials), each article was reviewed, although only one data abstraction form was used to avoid overrepresenting a single study population.

STATISTICAL ANALYSIS

We analyzed controlled trials and uncontrolled trials separately. Statistical testing for homogeneity was performed for each planned meta-analysis. Based on the results of this testing and clinical variation realized during data abstraction, a random-effects model was used to combine data for all outcomes. In combining data across studies, we weighted studies by the reciprocal of their SE and expressed results as pooled estimates with 95% confidence intervals (CIs). For controlled trials, weighted mean pooled differences between treated and control groups were calculated for each growth variable (eg, growth velocity and height SD score) at baseline and at time points representing short-(1-year) and long-term (adult height) outcomes. For uncontrolled trials, weighted mean pooled estimates for each growth variable before and after treatment were calculated. Growth data for controlled trials were therefore reported primarily as differences between treatment and control groups, whereas data for uncontrolled studies are reported primarily as the mean for the single group under study.

Because all studies did not report all outcome measures, we performed 2 main types of analyses for each growth variable. First, we calculated a pooled estimate across all studies reporting each growth variable (eg, in assessing baseline growth velocity in controlled studies, we pooled the differences in growth velocities between treatment and control groups across all 8 studies reporting this measure), subsequently referred to as an “aggregate analysis.” Second, we limited pooling of the baseline growth variable to the subgroup of studies that also reported the variable as an outcome (eg, for growth velocity in controlled trials, we pooled only the 6 studies reporting this measure at baseline and after 1 year); this second method yields a more direct comparison between baseline and the major postintervention periods and is subsequently referred to as a “paired analysis.” To assess the robustness of the results, several additional analyses were conducted, including analyses of the subgroup of controlled studies that were randomized; paired analyses in which only studies reporting baseline and outcome measures for each growth variable were included; and analyses of within-group (ie, treatment or control) changes in growth variables from baseline to follow-up, using the SDs for the pretreatment and posttreatment phases and their correlations, which were estimated from available data. For calculation of the latter correlations, we used the following formula:

\[ \text{Var}(x-y) = \text{Var}(x) + \text{Var}(y) - 2\text{rSD}(x)\text{SD}(y), \]

where \( \text{Var}(x-y) \) is the variance for the change between the pretreatment and posttreatment periods, \( \text{Var}(x) \) is the variance for the baseline period and \( \text{SD}(x) \) is the SD, \( \text{Var}(y) \) is the variance for the posttreatment period and \( \text{SD}(y) \) is the SD, and \( r \) is the correlation between the pretreatment and posttreatment values. For controlled and uncontrolled trials, we also determined that the aggregate (or pooled) results were robust by omitting the study with the largest sample size (and, separately, the study with the most extreme results) and then recalculating the effect size.

CONTROLLED TRIALS

The 10 controlled trials involved a total of 434 children; 6 were randomized controlled trials (239 children) and 4 were nonrandomized (195 children) (Table 1). There was little or no information about the method of randomization or masking. Baseline data for demographic variables were similar for the treatment and control groups. The weighted pooled estimate for age at baseline was 10.1±0.6 years in the treatment group and 9.8±0.7 years in the control group. Growth variables reported in each of the studies are given in Table 1. Table 2 gives the results of the meta-analysis for controlled studies of idiopathic short stature. The short-term (1-year) effects of GH treatment on growth velocity and height SD score were assessed, as were the long-term effects of GH on adult height; these are the primary outcome measures. Results for each growth variable are expressed as the pooled estimate of the difference between the treatment and control groups.

Effect of Short-term (1-Year) GH Therapy on Growth Velocity

Baseline pretreatment growth velocities of treatment and control groups were equivalent (pooled difference between treatment and control groups: -0.05±0.15 cm/y; Table 2), with respective mean baseline growth rates of 4.22±0.21 and 4.30±0.25 cm/y. Similarly, for the 6 studies reporting baseline and 1-year growth velocity, growth velocity at baseline was equal in treatment and control groups (pooled difference of 0.08±0.14 cm/y; Table 2). After 1 year, however, growth velocity was significantly greater in the GH-treated group than in controls; the pooled estimate for the difference in growth velocity between the 2 groups was 2.86±0.37 cm/y (Table 2). As shown in Figure 1, there was consistency among individual studies. In the 2 studies reporting data after 2 years of GH use, growth velocity in the treatment group remained greater than in controls (pooled difference between treatment and control groups, 2.36±0.36 cm/y).

Meta-analysis of the randomized controlled trials was consistent with that for all controlled trials. For the sub-
set of 5 randomized studies reporting baseline and 1-year outcome data, the difference in growth velocity between treatment and control groups was not significant at baseline (−0.08 cm/y [95% CI, −0.44 to 0.28]); however, after 1 year, the growth velocity of the GH-treated group exceeded that of controls by 2.53 cm/y (95% CI, 1.72–3.35).

In addition to the primary analyses comparing differences between treatment and control groups, we also assessed the change in growth velocity from baseline to 1 year. For the GH-treated group, the pooled change in growth velocity from baseline to 1 year was 3.63 ± 0.32 cm/y (95% CI, 3.00–4.25 cm/y), whereas for the control group, the change in growth velocity was only 0.93 ± 0.35 cm/y (95% CI, 0.25–1.62 cm/y). These results indicate that the GH-treated group experienced a significantly greater increment in growth velocity, and they are consistent with the analyses of the aggregate data, paired data, and randomized trials.

Effect of Short-term (1-Year) GH Therapy on Height SD Score

At baseline, the mean SD scores for height in the treatment and control groups were equivalent (difference between treatment and control groups = 0.02 SD; 9 studies [One article that otherwise met entry criteria was not included in this analysis because of a significant difference between baseline height SD scores in the treatment and control groups.]) (Table 2), and were similar for the 2 paired randomized controlled studies with 1-year data. However, after 1 year, the height of the GH-treated group exceeded that of the control group by 0.60 SD (Table 2).

Effect of GH Therapy on Adult Height

Four controlled trials reported data on adult height. The mean duration of treatment was 5.3 years. At baseline, the mean height SD scores for GH-treated and control groups were equivalent. However, the adult height achieved by the GH-treated group significantly exceeded that of controls, with a weighted aggregate difference in height between treatment and control groups of 0.84 SD (Table 2). In the GH-treated group, the pooled estimate for adult height was −1.51 SDs (95% CI, −1.70 to −1.32 SDs), whereas in the control group, adult height was significantly shorter at −2.29 SDs (95% CI, −2.63 to −1.96 SDs). (Some articles assess the effect of GH by comparing height SD score at baseline with that in adulthood. We did not use this approach because the current

Table 1. Controlled Trials of GH Therapy in Idiopathic Short Stature: Study Characteristics*

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Patients, No.</th>
<th>Age at Baseline, Mean ± SD, y</th>
<th>Males, %</th>
<th>Pubertal Status at Baseline</th>
<th>GH Dose, mg/kg per Week/Frequency, Injections/wk</th>
<th>Growth Variables Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td>Treatment</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCaughey et al,57 1998†</td>
<td>21</td>
<td>19</td>
<td>7.8 ± .52</td>
<td>7.7 ± .51</td>
<td>52 60</td>
<td>Prepubertal</td>
</tr>
<tr>
<td>Soliman and abdul Khadir,51 1996</td>
<td>12</td>
<td>12</td>
<td>7.2 ± 1.6</td>
<td>6.7 ± 1.4</td>
<td>NA NA</td>
<td>Prepubertal</td>
</tr>
<tr>
<td>Volta et al,53 1993</td>
<td>6</td>
<td>6</td>
<td>12 ± 0.3</td>
<td>12 ± 0.5</td>
<td>67 50</td>
<td>Pubertal</td>
</tr>
<tr>
<td>Volta et al,53 1991</td>
<td>10</td>
<td>10</td>
<td>10.9 ± 1.7</td>
<td>9.4 ± 2.1</td>
<td>NA NA</td>
<td>Prepubertal</td>
</tr>
<tr>
<td>Wit et al,54,55 1989</td>
<td>14</td>
<td>8</td>
<td>10 ± 1.5</td>
<td>9.4 ± 1.4</td>
<td>56 75</td>
<td>Prepubertal</td>
</tr>
<tr>
<td>Genentech Collaborative Study Group,56 1993</td>
<td>58</td>
<td>63</td>
<td>9.4 ± 1.9</td>
<td>9.5 ± 2.4</td>
<td>73 74</td>
<td>Prepubertal</td>
</tr>
<tr>
<td>Buchlis et al,58 1998</td>
<td>36</td>
<td>58</td>
<td>11.9 ± 2.8</td>
<td>12.5 ± 2.5</td>
<td>83 71</td>
<td>Mixed</td>
</tr>
<tr>
<td>Hindmarsh and Brook,59 1996§</td>
<td>16</td>
<td>10</td>
<td>8.4 ± 1.9</td>
<td>7.6 ± 1.5</td>
<td>63 60</td>
<td>Prepubertal</td>
</tr>
<tr>
<td>Lanes,60 1995</td>
<td>32</td>
<td>15</td>
<td>11.1 ± 2.2</td>
<td>10.7 ± 2.4</td>
<td>69 73</td>
<td>Prepubertal</td>
</tr>
<tr>
<td>Zadik et al,62 1992</td>
<td>11</td>
<td>17</td>
<td>12.8 ± 1.3</td>
<td>12.5 ± 1.7</td>
<td>100 100</td>
<td>Mixed</td>
</tr>
</tbody>
</table>

*The first 6 studies are randomized trials and the last 4 are nonrandomized trials. GH indicates growth hormone; GV, growth velocity; NA, not available; and PAH, predicted adult height.
†Includes references 57 to 61.
‡Includes references 54, 55, and 74 to 79; study reported 1-year GV via randomized controlled trial. Because of a change in study design after 1 year (all children were then treated with GH), data beyond 1 year are included under uncontrolled trials.
§Includes references 63 to 66.
data and previous work indicate that the adult height SD score often exceeds that in childhood, even for children with idiopathic short stature who do not receive GH.) Similarly, for the group of studies with paired data, adult height in the treated group exceeded that in controls by 0.78 SD (Table 2). Based on the US population, these data indicate an average difference in adult height between treatment and control groups of 5 to 6 cm (range, 2.3-8.7 cm).

In addition to comparing adult height of GH-treated and control groups, we also compared adult height achieved with that predicted at baseline. Data for individual studies are shown in Figure 1B, and results of the meta-analyses are given in Table 2. For the aggregate analysis, pooled predicted adult height was similar but not identical in treatment and control groups (−1.76±0.08 and −2.01±0.14 SDs, respectively), so that the GH-treated group was predicted to be approximately 0.3 SDs taller than the control group as adults (Table 2). However, for the 3 paired studies reporting predicted and achieved adult heights, the baseline predictions for treatment and control groups were similar (−1.73±0.10 and −1.85±0.13 SDs, respectively), and the pooled difference in predicted adult height SD score was 0.13 (Table 2). Yet, the GH-treated group reached adult heights that were 0.78 SD greater than controls, as described in the previous paragraph. These data suggest that the adult height achieved by the GH-treated group exceeds that predicted at baseline by 0.54 SD (aggregate data) to 0.65 SD (paired data), or 3.6 to 4.6 cm.

**UNCONTROLLED TRIALS**

Twenty-eight uncontrolled trials of GH therapy for idiopathic short stature (reported in 34 published articles and involving 655 children) met the entry criteria (Table 3). The pooled mean age of the patients was 10.8±0.4 years. The proportion of males ranged from 0% to 100%, with a mean of 71%. Figure 2 shows the results of individual trials included in the meta-analysis. Table 4 gives the results of the meta-analysis.

**Effect of Short-Term (1-Year) GH Therapy on Growth Velocity**

The pooled estimate of baseline growth velocity was 4.29±0.15 cm/y for the 21 studies reporting this measure (Table 4). In the paired analysis of 14 studies reporting baseline and 1-year data, growth velocity was the same at baseline and rose significantly to 7.57±0.30 cm/y after 1 year of GH treatment; the increase in growth velocity after 1 year of GH use in uncontrolled trials is similar to the difference in growth rates between treated and untreated groups.

**Table 2. Results of Meta-analysis for Controlled Trials of GH Therapy in Idiopathic Short Stature**

<table>
<thead>
<tr>
<th>Growth Variable</th>
<th>Patients (N)</th>
<th>Difference Between Treatment and Control Groups: Pooled Estimate, Mean ± SD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth velocity, cm/y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Aggregate 298 (8)</td>
<td>−0.05 ± 0.15 (−0.34 to 0.24)</td>
</tr>
<tr>
<td></td>
<td>Paired† 229 (6)</td>
<td>0.08 ± 0.14 (−0.20 to 0.37)</td>
</tr>
<tr>
<td></td>
<td>1 y 229 (6)</td>
<td>2.86 ± 0.37 (2.13 to 3.59)</td>
</tr>
<tr>
<td>Childhood height SD score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Aggregate 408 (9)</td>
<td>0.02 ± 0.05 (−0.08 to 0.12)</td>
</tr>
<tr>
<td></td>
<td>Paired† 36 (2)</td>
<td>0.12 ± 0.11 (−0.09 to 0.33)</td>
</tr>
<tr>
<td></td>
<td>1 y 36 (2)</td>
<td>0.60 ± 0.18 (0.26 to 0.95)</td>
</tr>
<tr>
<td>Adult height SD score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted</td>
<td>Aggregate 118 (4)</td>
<td>0.30 ± 0.12 (0.07 to 0.53)</td>
</tr>
<tr>
<td></td>
<td>Paired† 106 (3)</td>
<td>0.13 ± 0.16 (−0.18 to 0.44)</td>
</tr>
<tr>
<td>Achieved</td>
<td>Aggregate 125 (4)</td>
<td>0.84 ± 0.19 (0.46 to 1.22)</td>
</tr>
<tr>
<td></td>
<td>Paired† 112 (3)</td>
<td>0.78 ± 0.22 (0.35 to 1.21)</td>
</tr>
</tbody>
</table>

*GH indicates growth hormone; CI, confidence interval. Paired indicates analysis of only those studies reporting this variable at baseline and follow-up.

**Table 3**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>Study</th>
<th>Patients (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volta et al,1993</td>
<td>234</td>
<td>Soliman and Abdul Khadir,1996</td>
<td>187</td>
</tr>
<tr>
<td>Will et al,1989</td>
<td>34</td>
<td>Senette Collaborative Study Group,1989</td>
<td>36</td>
</tr>
<tr>
<td>McCaughhey et al,1998</td>
<td>120</td>
<td>Zadik et al,1992</td>
<td>100</td>
</tr>
<tr>
<td>Hindmarsh and Brook,1996</td>
<td>120</td>
<td>Buchlis et al,1998</td>
<td>100</td>
</tr>
<tr>
<td>Zadik et al,1992</td>
<td>100</td>
<td>McCaughhey et al,1998</td>
<td>100</td>
</tr>
</tbody>
</table>

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untreated groups in controlled studies. Results were similar for the 5 studies in which all patients were prepubertal at baseline and at 1-year follow-up. With continued GH treatment, growth velocity was 7.54 ± 0.17 and 5.81 ± 1.42 cm/y during the second and third years of treatment, respectively (2 studies for each year).

Effect of Short-term GH Therapy on Height SD Score

At baseline, the height SD score for 25 studies was −2.72. In the 10 studies reporting baseline and 1-year data, the height SD score at baseline was similar (−2.62), and it increased significantly to −2.19 after 1 year of GH treatment.

Table 3. Uncontrolled Trials of GH Therapy in Idiopathic Short Stature: Study Characteristics

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Patients, No.</th>
<th>Age at Baseline, Mean ± SD, y</th>
<th>Pubertal Status at Baseline</th>
<th>GH Dose, mg/kg per wk/Frequency, Injections/wk</th>
<th>Growth Variables Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasquino et al,71 2000</td>
<td>12</td>
<td>10.7 ± 1.0</td>
<td>0 Pubertal</td>
<td>0.30/6</td>
<td>Height: PAH, AH (4.9 y of treatment)</td>
</tr>
<tr>
<td>Hintz, for the Genentech Collaborative Group,78 1998†</td>
<td>92</td>
<td>9.8 ± 2.0</td>
<td>59 Prepubertal</td>
<td>0.30/6</td>
<td>GH: baseline, 1, 2 y</td>
</tr>
<tr>
<td>Hershkovitz et al,72 1998</td>
<td>10</td>
<td>NA</td>
<td>80 Prepubertal</td>
<td>0.23/6</td>
<td>Height: baseline, 3 y, PAH, AH (3 y of treatment)</td>
</tr>
<tr>
<td>Zadik and Zung,73 1997</td>
<td>16</td>
<td>11.0 ± 1.2</td>
<td>63 Prepubertal</td>
<td>0.25/6</td>
<td>Height: baseline, PAH, AH (4.5 y of treatment)</td>
</tr>
<tr>
<td>Bernasconi et al,74 1997</td>
<td>71</td>
<td>12.0 ± 0.2</td>
<td>76 Mixed</td>
<td>0.26/6</td>
<td>Height: baseline, 1-3 y, PAH, AH (4.2 y of treatment)</td>
</tr>
<tr>
<td>Schmitt et al,75 1997</td>
<td>17</td>
<td>9.5 ± 2.6</td>
<td>82 Prepubertal</td>
<td>0.36 or 0.24/6</td>
<td>Height: baseline, 1, 2, and 3 y; PAH; AH (5 y of treatment)</td>
</tr>
<tr>
<td>Spagnoli et al,76 1996</td>
<td>13</td>
<td>9.4 ± 1.6</td>
<td>77 Prepubertal</td>
<td>0.2/6</td>
<td>GH: baseline, 1 y</td>
</tr>
<tr>
<td>Zadik et al,77 1996</td>
<td>30</td>
<td>12.1 ± 1.3</td>
<td>70 Prepubertal</td>
<td>0.23/6</td>
<td>Height: baseline, AH (4.5 y of treatment)</td>
</tr>
<tr>
<td>Lopez-Sigueri et al,78 1996</td>
<td>20</td>
<td>11.4 ± 1.3</td>
<td>100 NA</td>
<td>0.17-0.25/6</td>
<td>GH: baseline, AH, PAH, AH (5.3 y of treatment)</td>
</tr>
<tr>
<td>Chalew et al,79 1996</td>
<td>8</td>
<td>10.3 ± 2.8</td>
<td>62 Mixed</td>
<td>0.3/3</td>
<td>GH: baseline, 6 mo</td>
</tr>
<tr>
<td>Spagnoli et al,80 1995‡</td>
<td>67</td>
<td>9.0 ± 1.7</td>
<td>66 Prepubertal</td>
<td>0.19/6</td>
<td>GH: baseline, 6 mo</td>
</tr>
<tr>
<td>Low et al,81 1994</td>
<td>11</td>
<td>8.6 ± 2.4</td>
<td>73 Prepubertal</td>
<td>0.23/6</td>
<td>GH: baseline, 1 y</td>
</tr>
<tr>
<td>Zadik et al,82 1994</td>
<td>43</td>
<td>9.9 ± 5.1</td>
<td>100 Mixed</td>
<td>0.3/3</td>
<td>GH: baseline, 1 y</td>
</tr>
<tr>
<td>Azzarito et al,83 1994</td>
<td>11</td>
<td>13.3 ± 1.6</td>
<td>73 NA</td>
<td>0.16/6</td>
<td>GH: baseline, 1 y</td>
</tr>
<tr>
<td>Job et al,84 1994</td>
<td>15§</td>
<td>13.1 ± 1.6</td>
<td>47 Pubertal</td>
<td>0.2/6</td>
<td>GH: baseline, 1, 2 y</td>
</tr>
<tr>
<td>Loche et al,85 1994</td>
<td>8</td>
<td>11.8 ± 0.8</td>
<td>75 Prepubertal</td>
<td>0.3/6</td>
<td>GH: baseline, 1 y</td>
</tr>
<tr>
<td>Zadik et al,86 1993</td>
<td>34§</td>
<td>9.0 ± 0.8</td>
<td>82 Prepubertal</td>
<td>0.27/3</td>
<td>GH: baseline, 1 y, AH (4 y of treatment)</td>
</tr>
<tr>
<td>Bierich et al,87 1992</td>
<td>15</td>
<td>12.7 ± 2.6</td>
<td>87 Mixed</td>
<td>0.18/3</td>
<td>GH: baseline, 6 mo, 1 y</td>
</tr>
<tr>
<td>Low and Lau,88 1992</td>
<td>7</td>
<td>7.5 ± 2.0</td>
<td>71 Prepubertal</td>
<td>0.33/6</td>
<td>GH: baseline, 1 y</td>
</tr>
<tr>
<td>Zadik et al,89 1992</td>
<td>15</td>
<td>9.1 ± 1.9</td>
<td>74 Prepubertal</td>
<td>0.23/6</td>
<td>GH: baseline, 1 y</td>
</tr>
<tr>
<td>Colle et al,90 1990</td>
<td>9§</td>
<td>14.9 ± 1.3</td>
<td>67 Pubertal</td>
<td>0.27/6</td>
<td>GH: baseline, 6 mo, 1 y</td>
</tr>
<tr>
<td>Chanoine et al,91 1991</td>
<td>40</td>
<td>10.4</td>
<td>63 Prepubertal</td>
<td>0.24/6</td>
<td>GH: baseline, 6 mo, 1 y</td>
</tr>
<tr>
<td>Hernandez et al,92 1991</td>
<td>16</td>
<td>9.5 ± 1.6</td>
<td>75 Prepubertal</td>
<td>0.17/6</td>
<td>GH: baseline, 6 mo, 1 y</td>
</tr>
<tr>
<td>Loche et al,93 1991</td>
<td>8</td>
<td>13.7 ± 1.4</td>
<td>100 Mixed</td>
<td>0.2/6</td>
<td>GH: baseline, 6 mo</td>
</tr>
<tr>
<td>Rochiccioli et al,94 1990</td>
<td>24</td>
<td>10.8</td>
<td>58 Mixed</td>
<td>0.14/3/6</td>
<td>GH: baseline, 1 y</td>
</tr>
<tr>
<td>Schwartz et al,95 1990</td>
<td>5</td>
<td>12.5 ± 1.6</td>
<td>60 Prepubertal</td>
<td>0.23/6</td>
<td>GH: baseline, 1 y</td>
</tr>
<tr>
<td>Darendeliler et al,96 1990</td>
<td>27</td>
<td>8.3 ± 2.2</td>
<td>67 Prepubertal</td>
<td>0.14-0.35/6</td>
<td>GH: baseline, 1 y</td>
</tr>
<tr>
<td>Lin et al.,97 1989</td>
<td>28</td>
<td>11.1 ± 2.0</td>
<td>NA Mixed</td>
<td>0.3/3</td>
<td>GH: baseline, 6 mo</td>
</tr>
</tbody>
</table>

*GH indicates growth hormone; PAH, predicted adult height; AH, adult height (mean years of treatment); GV, growth velocity; and NA, not available.
†Includes references 74 to 79. Study reported 1-year GV via randomized controlled trial, and these data are included in Tables 1 and 2. Because of a change in study design after 1 year (all children were then treated with GH), data beyond 1 year are included under uncontrolled trials.
‡Includes references 87 and 88.
§Reported data were separated by either sex or timing of GH administration; data were combined using a weighted average for analyses.
The mean duration of treatment was 4.7 years. At baseline, the mean predicted adult height was based on comparison of adult height achieved with that predicted at baseline (individual trial data are shown in Figure 2; the meta-analysis data are addressed in Table 4). Results for the paired analyses (n=6) were similar, with predicted adult height at baseline of −2.25 SDs, whereas the height actually achieved after GH therapy was greater at −1.62 SDs (Table 4). The results for the controlled trials (n=17) were similar, with predicted adult height at baseline of −2.52 to −1.85 SDs, whereas the height actually achieved after GH therapy was greater at −1.60 SDs (Table 4). The data suggest a difference of 0.56 to 0.63 SD, or 3.8 to 4.5 cm, between predicted height before GH therapy and attained height after GH therapy. These results are similar to those for the controlled trials. We reanalyzed the data with omission of the trials with largest sample size or largest effect size, and the results were unchanged.

**Effect of Long-term GH Therapy on Adult Height**

In uncontrolled trials, the assessment of effect of GH on adult height was based on comparison of adult height achieved with that predicted at baseline (individual trial data are shown in Figure 2; the meta-analysis data are given in Table 4). The mean duration of treatment was 4.7 years. At baseline, the mean predicted adult height was −2.18 SDs; in the aggregate analysis, after GH treatment, the adult height attained was significantly greater at −1.62 SDs (Table 4). Results for the paired analyses (n=6) were similar, with predicted adult height at baseline of −2.25 SDs, whereas the height actually achieved after GH therapy was greater at −1.62 SDs (Table 4). The data suggest a difference of 0.56 to 0.63 SD, or 3.8 to 4.5 cm, between predicted height before GH therapy and attained height after GH therapy. These results are similar to those for the controlled trials. We reanalyzed the data with omission of the trials with largest sample size or largest effect size, and the results were unchanged.

**Figure 2.** Results of individual uncontrolled trials of growth hormone therapy for idiopathic short stature included in the meta-analysis. For a complete listing of author names, reference citation, and study year, see Table 3. A, Mean±SE growth velocity at baseline and after 1 year. Asterisk indicates that this study addressed the effect of growth hormone treatment in older children during the decelerating phase of the pubertal growth spurt. B, Mean adult height SD scores achieved with that predicted at baseline (individual trial data are shown in Figure 2; the meta-analysis data are addressed in Table 4). The mean duration of treatment was 4.7 years. At baseline, the mean predicted adult height was based on comparison of adult height achieved with that predicted at baseline (individual trial data are shown in Figure 2; the meta-analysis data are addressed in Table 4). The mean duration of treatment was 4.7 years. At baseline, the mean predicted adult height was based on comparison of adult height achieved after 1 year of growth hormone therapy. A fundamental issue in the debate about GH treatment for idiopathic short stature is uncertainty about its degree of effectiveness in promoting growth. This meta-analysis shows that 1 year of GH therapy causes a clear increase in growth velocity and suggests that long-term GH therapy increases adult height in children with idiopathic short stature. The adult height achieved by GH-
treated individuals exceeded that of untreated controls by 0.78 to 0.84 SD. Similarly, comparisons of predicted and achieved adult height in controlled and uncontrolled trials show a gain of 0.54 to 0.65 SD. The weight of the evidence, therefore, indicates that GH treatment increases short-term growth velocity and can increase adult height in idiopathic short stature.

Limitations of this analysis deserve comment. One potential limitation of any meta-analysis is pooling studies with heterogeneous populations. However, the rigorous entry criteria and review procedures for the current analyses were instituted to exclude studies in which patients had known causes of short stature. A second potential limitation involves the effect of study dropouts on the validity of study findings. To minimize this effect, we excluded any study with a dropout rate of 50% or greater; 27 of 38 qualifying studies for idiopathic short stature had no dropouts and, of the remainder, the mean dropout rate was 20%. Nevertheless, there remains the possibility that, particularly for uncontrolled studies, effects may differ in children lost to follow-up. A third potential limitation is the use of uncontrolled studies, since unrecognized variables may affect results. However, in situations in which randomized controlled studies are limited and the field requires evidence-based analyses, a rigorous approach including observational studies is indicated.49,101 We followed guidelines for such meta-analyses, analyzed controlled and uncontrolled trials separately, and, whenever possible, triangulated conclusions using both analyses. A fourth potential limitation of any meta-analysis is the “file drawer” effect, in which studies with negative results might remain unpublished, tending to bias the published literature toward positive findings. We attempted to minimize this bias by examining sources of unpublished studies and by having independent GH experts review the list of studies to ensure that all trials meeting entry criteria—published or unpublished—were included.

The results of these analyses have implications for clinical practice and health policy. Much of the debate about GH use for children with idiopathic short stature has centered on whether treatment actually increases adult height. The current findings indicate that long-term GH treatment can increase adult height. These results, therefore, suggest that the emphasis and debate shift to whether the gain in adult height is of sufficient clinical importance and value to warrant more widespread treatment of short children. In controlled trials, the average adult height SD score achieved after GH therapy was 1.51 (ie, 166.5 cm for US males and 153.5 cm for US females), whereas that for untreated controls was 2.29 (ie, 160.7 cm in males and 148.3 cm in females).16 Similarly, the difference between adult height of GH-treated and control groups was 0.78 to 0.84 SD, or 5 to 6 cm (range, 2.3-8.7 cm). The difference between predicted and attained height in controlled and uncontrolled trials of GH (0.34-0.65 SD) similarly suggests a gain of 4 to 5 cm in adult height from GH therapy.

Practitioners and policy makers now need to address the clinical importance and value of the height gained in relation to the goals of treatment. Consideration of additional factors will be important for deciding whether GH should be used for idiopathic short stature in practice, including the impact of the height gained on physical and psychosocial well-being, adverse effects, cost of therapy, patients’ expectations and values, and ethical considerations.* To date, adverse effects of GH (including fluid retention, benign intracranial hypertension, insulin resistance, and growth of nevi10,108,109) have been reported in a few patients, and long-term surveillance is ongoing. In the trials included in the current analyses, mild increases in serum insulin levels and/or the presence of GH antibodies were occasionally reported.36,60,63,68 Although a full economic analysis is beyond the scope of this article, cost and resource allocation have been core concerns for GH treatment; a gain of 4 to 6 cm in adult height, together with an average of 5 years of GH therapy beginning at age 10 years, and prices of $11000 to $18000/y as the child grows,2,25,110 corresponds to more than $35000 per 2.54 cm gained. The ethical issues are also significant.6,10,13 Short stature may be seen as disabling, and taller stature may be associated with improved quality of life.102-107; in this sense, treatment of idiopathic short stature may be considered appropriate, particularly with difficulty reaching consensus on clinical and/or biochemical criteria for GH use. Alternatively, GH treatment may be considered inappropriate for short, otherwise healthy children.

The data on short-term effects of GH in idiopathic short stature also are relevant for practice. The increase in growth velocity observed during the first year of GH treatment raises questions about the practical application of 6- to 12-month therapeutic trials of GH in individual patients as a method to determine their need for long-term GH therapy.1-8,9,25,110 Because even the lower end of the observed range for growth velocity exceeds many recommended thresholds for considering such trials successful.

In a separate meta-analysis, we found in children with classic GH deficiency that growth velocity increased from 3.61±0.12 cm/y at baseline to 9.77±0.18 cm/y after 1 year of GH treatment and that height increased from −3.47±0.31 SDs to −2.51±0.11 SDs during that time, confirming earlier results in this population.111,112 Although it may be tempting to consider growth velocity after 1 year of treatment in GH deficiency as exceeding that for idiopathic short stature (and therefore capable of differentiating the 2 conditions), this is not warranted because the data are based on separate studies rather than on direct comparisons of GH effectiveness for the conditions.

This analysis has also illuminated gaps in the literature that can affect interpretation of data on the effectiveness of GH therapy and suggests areas for future research. First, standardization of reporting requirements for clinical studies of GH treatment (eg, inclusion of predicted and midparental heights, baseline and outcome growth velocity, and height SDs) would enhance the clarity of results for clinicians and researchers. Second, although we used standard definitions of classic GH deficiency and idiopathic short stature,1,10,16,25,36,37,111 few studies meeting the entry criteria also reported supple-

*References 6, 10, 13, 16, 58, 79, 102-108.
Growth hormone (GH) has been suggested as a potential treatment for children with idiopathic short stature, a condition affecting many US children. Its use for idiopathic short stature is highly controversial, in part because its efficacy in promoting growth in this condition is not known.

We performed a systematic, meta-analytical review of all controlled and uncontrolled studies in the literature meeting strict entry criteria to define the short- and long-term effects of GH in children with idiopathic short stature. The results indicate that GH has a strong short-term growth-promoting effect and can increase adult height for this condition. These data provide evidence of GH efficacy and indicate that GH therapy, on average, increases adult height by 4 to 6 cm for children with idiopathic short stature. The results raise fundamental questions about the use of therapeutic trials of GH and the impact of height gained on well-being.

**What This Study Adds**

The results of this study indicate that GH therapy augments short- and long-term responsiveness to GH therapy in individual patients. In summary, this analysis addresses the fundamental issue of the effectiveness of GH for promoting growth in children with idiopathic short stature. The results indicate that GH therapy augments short- and long-term growth. These data are necessary to inform clinical decision making and policy. However, alone they are not sufficient to define the clinical value of treatment. We believe that the focus of assessment should increasingly shift from efficacy in promoting growth to effectiveness in promoting health and well-being as a function of increased growth. Use of GH will ultimately depend on its efficacy in increasing height, along with the morbidity of the treated and untreated states, and on the value of the height gain to families, physicians, third-party payers, and society.

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