Growth Hormone Therapy for Children Born Small for Gestational Age: Height Gain Is Less Dose Dependent Over the Long Term Than Over the Short Term

Francis de Zegher, MD, PhD*, and Anita Hokken-Koelega, MD, PhD‡

ABSTRACT. Background. Approximately 3% of children are born small for gestational age (SGA), and ~10% of SGA children maintain a small body size throughout childhood and often into adult life. Among short SGA children, growth hormone (GH) therapy increases short-term growth in a dose-dependent manner; experience with long-term therapy is limited.

Objective. To delineate the dose dependency of long-term height gain among short SGA children receiving GH therapy.

Methods. We performed an epianalysis of the first adult height data for SGA children (n = 28) enrolled in 3 randomized trials comparing the growth-promoting efficacy of 2 continuous GH regimens (33 or 67 μg/kg per day for ~10 years, starting at ~5 years of age); in addition, we performed a meta-analysis of the adult height results published previously and those presented here.

Results. Epianalysis outcomes (n = 28) suggested that adult height increased more with a higher-dose regimen than with a lower-dose regimen. In the meta-analysis (n = 82), the higher-dose regimen was found to elicit a long-term height gain superior to that achieved with the lower-dose regimen by a mean of 0.4 SD (~1 inch). Children who were shorter at the start of therapy experienced more long-term height gain.

Conclusions. These findings confirm GH therapy as an effective and safe approach to reduce the adult height deficit that short SGA children otherwise face. In addition, the first meta-analysis indicated that height gain is less dose dependent over the long term than over the short term, at least within the dose range explored to date. For SGA children whose stature is not extremely short, current data support the use of a GH dose of ~33 μg/kg per day from start to adult height, particularly if treatment starts at a young age; shorter children (for example, height below ~3 SD) might benefit from an approach in which short-term catch-up growth is achieved with a higher dose (~50 μg/kg per day) and long-term growth to adult height is ensured with a GH dose of ~33 μg/kg per day. Because GH-induced accelerations of height and weight gain evolve in parallel, the dose tapering from ~50 μg/kg to ~33 μg/kg can be accomplished by simply maintaining the absolute GH dose (in micrograms) while the child gains weight (in kilograms). With this algorithm, more growth-responsive children taper their GH dose down to ~33 μg/kg per day more quickly. Pediatrics 2005;115:468–462. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1934; growth hormone, small for gestational age, growth, intrauterine growth retardation, short stature, adult height.

ABBREVIATIONS. SGA, small for gestational age; SDS, SD score (z score); GH, growth hormone; ANCOVA, analysis of covariance.

By definition, ~3% of children are born small for gestational age (SGA) (SD score [SDS] below ~2 for weight and/or length at preterm or term birth). Most SGA infants exhibit sufficient postnatal catch-up growth to normalize their stature by the age of 2 years, regardless of whether they were born preterm or at term.1 Approximately 10% of SGA children maintain a small body size, defined as a height below ~2 SD throughout childhood; among adults with short stature, ~20% were born SGA.2

Growth hormone (GH) therapy, if started in middle childhood, increases short-term growth (over 1–5 years) in a dose-dependent manner.3–9 However, short-term bone maturation also accelerates in a dose-dependent manner; therefore, height gain into adulthood was long anticipated to be less dose dependent than height gain in childhood.5 This anticipation was corroborated by the first results with long-term GH therapy (~33 or ~67 μg/kg per day for 7–8 years, starting at ~8 years of age), which indicated not only that GH therapy is effective in increasing adult height but also that the dose dependency, if any, amounts to no more than ~0.3 SD when adult height is reached.10 The current consensus is that more adult height results are needed before recommendations regarding short- and long-term GH doses can be made.11,12

Here we report an epianalysis (based on individual data) of the first adult height results for SGA children who were enrolled in 3 randomized studies comparing the long-term growth-promoting efficacy of 2 GH doses (33 or 67 μg/kg per day for ~10 years; starting at ~5 years of age). In addition, we report a meta-analysis (based on group data) of the previous10 and present results on adult height; the addition of statistical power allowed us to delineate more clearly the limited dose dependency of the GH-induced gain in the adult height of short SGA children.
METHODS

Study Population and Design

In 1990, 3 randomized, multicenter studies were initiated to explore the effects of continuous GH treatment among non-GH-deficient SGA children who had failed to normalize their stature through spontaneous catch-up growth during infancy. The originally enrolled study populations in the Nordic countries (Denmark, Finland, Norway, and Sweden), Germany, and France (234 treated) were described in the reports of the results after 2, 4, and 6 years of GH therapy.5–7

The inclusion criteria were as follows: (1) birth weight or length below $-2$ SD for gestational age, (2) height below $-2$ SD for chronologic age, (3) height velocity below $0$ SD (France) or $-67$ SD (Germany and Nordic countries) for chronologic age, (4) chronologic age between 2 and 8 years (2–7 years for German girls and 2–9 years for Nordic boys), (5) prepubertal condition at the start of the study, (6) serum GH concentration of $>10$ µg/L in a random sample or after a GH stimulation test, and (7) written informed consent. The exclusion criteria were as follows: (1) endocrine or chronic disease; (2) previous or ongoing chemotherapy, radiotherapy, or GH or anabolic steroid treatment; or (3) chromosomal anomaly, skeletal dysplasia, severe mental retardation, or malformation syndrome, except for Silver-Russell, fetal alcohol, and Dubowitz syndromes (exceptions not applicable to France and Nordic countries).

Each of these 3 studies was originally designed as an open-label, controlled, multicenter trial over 2 years with 3 parallel groups assembled through weighted randomization.5–7 One group was not treated and 2 groups were treated with daily subcutaneous injections of human GH (Genotropin; Pfizer, Stockholm, Sweden) given at a dose of $33$ or $67$ µg/kg. None of the untreated control groups was maintained beyond 2 years of study.7 After the initial 2 years, the Nordic and German studies investigated the effects of continued GH treatment at a daily dose of $33$ or $67$ µg/kg. In France, continuous GH treatment at a daily dose of $33$ or $67$ µg/kg was available only to children who had failed to reach a height above $-1$ SD, irrespective of mid-parental height.7 Because of the study design in France, the adult height results obtained with continuous GH treatment in that trial were anticipated to be biased toward poor responsiveness, and they were taken into account only for the assessment of the dose dependency of gain in adult height.

In the present epianalysis, the additional criteria for inclusion were as follows: (1) end-pubertal growth velocity of $<4$ cm/year and (2) continuous GH treatment for $\geq 7.0$ years. Table 1 lists the additional exclusion criteria that ultimately defined the present study population ($n = 28$).

\[
\begin{array}{|l|c|c|c|c|c|c|}
\hline
\text{TABLE 1. Number of Patients Excluded From the Adult Height Analysis, Listed According to the Reason for Their Exclusion} & \text{Germany + Nordic} & \text{France} & \text{All} & \text{All} \\
\hline
\text{33 µg/kg per d} & \text{67 µg/kg per d} & \text{33 µg/kg per d} & \text{67 µg/kg per d} & \text{33 µg/kg per d} & \text{67 µg/kg per d} \\
\hline
\text{Randomized} & 45 & 53 & 73 & 63 & 118 & 116 & 234 \\
\text{Inclusion error} & 6 & 8 & 11 & 4 & 17 & 12 & 29 \\
\text{Withdrawal from study because of} & & & & & & & \\
\text{Adverse event} & 2* & 6† & 1 & 2 & 7 & 9 & \\
\text{Change in logistics of GH supply in 1 country} & 8 & 5 & 14 & 13 & 15 & 21 & 36 \\
\text{Noncompliance with treatment or follow-up} & 1 & 8 & & & & & \\
\text{monitoring} & & & 14 & 13 & & & \\
\text{Consent withdrawal} & 6 & 10 & 7 & 7 & 13 & 17 & 30 \\
\text{Duration of treatment of <7 y} & 2 & 3 & 2§ & 29 & 30 & 32 & 62 \\
\text{Growth velocity of >4 cm/ y at last visit} & 5 & 3 & 4 & 3 & 9 & 6 & 15 \\
\text{Height difference of <0.5 SD between child and} & 4 & 1 & 48 & 8 & 1 & 9 & \\
\text{a parent} & & & & & & & \\
\text{Height velocity at start of >0 SD} & 1 & & & 1 & 1 & 1 & 2 \\
\text{Birth weight above -1.5 SD} & 10 & 9 & 4 & 5 & 14 & 14 & 28 \\
\hline
\end{array}
\]

* Including 1 child with abnormal oral glucose tolerance test results after 3 months of GH therapy.
† Including 1 child with increased intracranial pressure after 7 years of GH therapy.
§ Including 2 children with average height of $\geq 2$ cm.

Statistical Analyses

The gain in adult height was analyzed with multivariate linear regression analyses. The analysis of covariance (ANCOVA) model included country (France, Germany, or Nordic countries) and GH dose as factors and height SD at the start of the study as a covariate. Other variables were presumed to have effects on the gain in adult height but they showed no detectable effect in this population (chronologic age at the start of GH therapy, percentage of time receiving GH therapy, and target height SD) or data were not available for all children (bone age delay at the start of GH therapy); therefore, these variables were excluded from the full model, to yield more degrees of freedom.

To increase statistical power in the analysis of dose dependency, we performed a meta-analysis that included the results from another randomized study, which used Norditropin (Novo

Study Methods

Study visits, including auxologic evaluations and dose adjustments, were scheduled at least every 6 months. The effects of GH administration on growth were assessed by determining changes in variables such as weight and height SDS, with and without adjustment for mid-parental height SDS, as described.7 The onset of puberty was defined for girls as breast stage of $\geq 2$ and for boys as testicular volume of $\geq 3$ mL.

The true gain in adult height is not known for the children in this study population, in part because we included children with ongoing growth at a rate of up to $4$ cm/year at the last recorded visit. The estimated gain in adult height was calculated as the difference between the height SD for adult normative values (using the upper reference age of 21 years)13 at the last recorded visit and the height SD for chronologic age at the start of treatment. To facilitate interpretation of the results, the gain in height SD was also converted into centimeters.

Initially, we analyzed the change in height SD for chronologic age from the start of treatment to the last recorded visit. This analysis, however, overestimated the true gain in adult height, because children had reached near-adult height without necessarily reaching adult age. Because adult height had not yet been reached by all children, the uniform use of height SD for adult normative values underestimated the change in height SD. Nevertheless, we used the latter normative values to compensate for not taking into account the spontaneous catch-up growth (an average of $0.3$–$0.4$ SD) that short SGA children are expected to exhibit if they remain untreated.14,15–19

The French, German, and Nordic protocols specified 3 childhood height references, which had different adult-age criteria. In this analysis, we used only 1 of these references,13 to harmonize the data from the 3 trials.
### TABLE 2. Clinical and Treatment Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Germany + Nordic</th>
<th>France</th>
<th>All</th>
<th>All (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33 µg/kg per d (N = 10)</td>
<td>67 µg/kg per d (N = 9)</td>
<td>33 µg/kg per d (N = 4)</td>
<td>67 µg/kg per d (N = 5)</td>
</tr>
<tr>
<td>Age at onset of puberty (boys, testes stage ≥2), y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.3 (1.4)</td>
<td>15.7 (1.0)</td>
<td>13.6</td>
<td>15.8 (1.4)</td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
<td>14.4 (12.5, 15.9)</td>
<td>16.2 (139, 164)</td>
<td>13.6 (13.6, 13.6)</td>
<td>15.4 (14.6, 174)</td>
</tr>
<tr>
<td>Age at last visit, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>15.6 (0.8)</td>
<td>17.1 (1.5)</td>
<td>16.4 (1.9)</td>
<td>16.8 (1.5)</td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
<td>15.5 (14.9, 17.0)</td>
<td>16.8 (156, 193)</td>
<td>17.1 (14.2, 179)</td>
<td>16.8 (157, 178)</td>
</tr>
<tr>
<td>Height velocity at last visit, cm/y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.1 (0.8)</td>
<td>1.1 (1.3)</td>
<td>2.1 (1.0)</td>
<td>0.9 (1.0)</td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
<td>2.0 (09.3, 3.6)</td>
<td>0.8 (0-3.32)</td>
<td>2.1 (10.32)</td>
<td>0.5 (0.3, 2.8)</td>
</tr>
<tr>
<td>GH dose actually given, µg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>31.0 (2.3)</td>
<td>59.8 (4.2)</td>
<td>33.4 (0.3)</td>
<td>59.1 (3.3)</td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
<td>31.7 (25.6, 33.4)</td>
<td>60.3 (516, 666)</td>
<td>33.3 (33.3, 337)</td>
<td>572.6 (632)</td>
</tr>
<tr>
<td>Duration of treatment, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10.2 (1.3)</td>
<td>10.1 (1.3)</td>
<td>10.5 (2.1)</td>
<td>9.2 (1.9)</td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
<td>10.4 (7.7, 12.1)</td>
<td>10.4 (7.6, 12.3)</td>
<td>10.7 (81.124)</td>
<td>8.5 (76.120)</td>
</tr>
</tbody>
</table>
Nordisk, Bagsvaerd, Denmark). In the latter study, adult height was reached by almost all children, another height reference was used, and the gain in adult height was estimated from the change in height SD for chronologic age between GH treatment start and the last recorded visit; in other words, adult height was not assessed with adult normative values. That study was analyzed with both a 2-sample t test and an ANCOVA, with the t test analysis being presented as the main analysis. The results from the t test were used in the meta-analysis, combined with the ANCOVA results from the Nordic, German, and French trials. In the meta-analysis, differences and SE values were combined into a weighed average.

RESULTS

Table 2 displays the clinical and treatment characteristics of the study population. At the start of treatment, the mean age of the children was ~5 years and their height was ~3 SD below the normative value for chronologic age; after adjustment for mid-parental height, their height was still ~2 SD below the normative value. The average duration of GH treatment was ~10 years. At the last recorded visit, the mean growth velocity was 1.6 cm/year. In the high-dose group, the GH amount given was ~10% below the intended study dose, partly because of underestimation of weight gain between study visits.

Table 3 displays the results of an ANCOVA of the increase in height SDS between the start of GH therapy and the last visit. The model accounts for 60% of the observed variance; shorter children gained more height. In France, the apparently lower efficacy of continuous GH therapy is likely attributable to the bias introduced by the study design.

Table 4 summarizes the long-term results, as well as the meta-analysis of the dose effect on the increase in height SDS between the start of GH treatment and the last visit. The outcomes among Nordic, German, and French children (n = 28) suggested that adult height increased more with the higher-dose regimen, compared with the lower-dose regimen. In the meta-analysis, the higher-dose regimen was confirmed to elicit a long-term height gain that was superior to that achieved with the lower-dose regimen by a mean of 0.4 SD (~1 inch, P = .019).

DISCUSSION

In the absence of randomized, control groups up to adult height, we estimated the GH-induced gain in the adult height of short SGA children by calculating the difference between height SDS at the start of GH therapy and at the last visit. This approach allowed us to estimate that long-term (~10-year) GH therapy reduced the adult height deficit of short SGA children; the long-term benefit proved less dose depen-

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**TABLE 3. Results of ANCOVA of Increase in Height SDS Between Start of GH Therapy and Last Recorded Visit (N = 28)**

<table>
<thead>
<tr>
<th>Regression Coefficient</th>
<th>SEM</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.11</td>
<td>0.55</td>
</tr>
<tr>
<td>Height SDS at start</td>
<td>0.53</td>
<td>0.15</td>
</tr>
<tr>
<td>GH dose, 67 vs 33 μg/kg per d</td>
<td>0.47</td>
<td>0.23</td>
</tr>
<tr>
<td>Country</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>-1.31</td>
<td>0.29</td>
</tr>
<tr>
<td>Germany</td>
<td>-0.55</td>
<td>0.28</td>
</tr>
<tr>
<td>Nordic</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

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**TABLE 4. Increase in Height Between Start of GH Therapy and Last Recorded Visit**

<table>
<thead>
<tr>
<th>Unit</th>
<th>33 μg/kg per d</th>
<th>67 μg/kg per d</th>
<th>Difference (67 μg/kg per d - 33 μg/kg per d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>N = 10; mean:</td>
<td>N = 10; mean:</td>
<td>N = 0; mean:</td>
</tr>
<tr>
<td>cm</td>
<td>11.3; SEM: 1.4</td>
<td>7.4; SEM: 1.4</td>
<td>3.9; 95% CI: 0.7 to 8.5; P = .088</td>
</tr>
<tr>
<td>cm</td>
<td>N = 14; mean:</td>
<td>N = 14; mean:</td>
<td>N = 14; mean:</td>
</tr>
<tr>
<td>cm</td>
<td>7.4; SEM: 1.4</td>
<td>3.1; SEM: 1.4</td>
<td>4.3; 95% CI: 0.1 to 8.2; P = .057</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
dent than the short-term growth acceleration evoked by GH therapy. These long-term findings were well in line not only with the short-term findings for the same cohorts3-5 but also with long-term findings for another cohort of SGA children who received similar GH doses in a comparable age range.9,10 Inevitably, the first adult height results for any long-term SGA cohort are biased toward those for children who started GH hormone therapy late and/or completed puberty earlier. Whether this bias resulted in an underestimation of the efficacy of GH in the present analysis will ultimately need to be clarified by adding to the present results those of early GH starters and/or late matures.

Shorter stature at the start of GH treatment was associated with more long-term height gain. Therefore, the most height gain was observed for the children who needed it most, as judged by their shortness of stature. Recently, the short-term growth response to GH among short SGA children was found to be higher for children with relatively low somatotropic activity and relatively high insulin sensitivity.22,23 Because pretreatment somatotropic activity and insulin sensitivity were not necessarily screened in the present studies, it remains to be determined to what extent a low height SDS at base-line reflects low somatotropic activity or an insulin-sensitive state among short SGA children.

CONCLUSIONS

Our findings confirm that GH therapy is an effective and safe approach to reduce the adult height deficit that short SGA children otherwise face; in addition, they confirm that height gain is less dose dependent over the long term than over the short term, at least within the dose range explored to date. For SGA children whose stature is not extremely short (for example, height above -3 SD), current data support the use of a GH dose of ~33 μg/kg per day from start to adult height, particularly if treatment is started at a young age (4–6 years). Shorter children (height below -3 SD) might benefit from an approach in which short-term catch-up growth is achieved with a higher dose (~50 μg/kg per day) and long-term growth up to adult height is ensured with a GH dose of ~33 μg/kg per day. Because GH-induced accelerations of height and weight gain evolve in parallel,5 dose tapering from ~50 mg/kg to ~33 μg/kg per day can be accomplished by simply maintaining the absolute GH dose (in micrograms) while the child gains weight (in kilograms). With this algorithm, more growth-responsive children taper their GH doses more quickly down to ~33 μg/kg per day.

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This manuscript is dedicated to Professor H.K.A.Visser.

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