Long-term results of growth hormone therapy in children with short stature, subnormal growth rate and normal growth hormone response to secretagogues


Departments of Paediatrics of the Universities of *Leiden, †Rotterdam, §Utrecht, ‡Nijmegen, ¶Amsterdam, ‖Juliana Children's Hospital in the Hague, **Catherina Hospital in Eindhoven and the ††Bureau of the Dutch Growth Foundation Leiden, The Netherlands.

(Received 14 July 1994; returned for revision 1 November 1994; finally revised 24 November 1994; accepted 23 December 1994)

It has been suggested that some children with idiopathic short stature (ISS), including familial short stature and/or constitutional delay, may have a low spontaneous GH secretion in contrast to normal serum GH responses to provocative testing, a condition called ‘GH neurosecretory dysfunction’ (Bereu et al.; Spiliotis et al., 1984). Although this term cannot be clearly defined, even less adequately than the term GH deficiency (GHD), GH secretion certainly varies among the children with ISS and it is suggested that some of these children may produce less GH than they need for adequate growth (Albertsson-Wikland & Rosberg, 1988; Zadik et al., 1992a). Theoretically, such children would increase their growth rate on a regular substitution dosage of GH, while children with an adequate GH secretion and a relative GH insensitivity would need a higher dosage to grow faster. This hypothesis is supported by the observation that GH treatment in various dosages leads to a significant acceleration of the average height velocity during the first years of treatment, though with a considerable inter-individual variation (Hopwood et al., 1993; Hindmarsh & Brook, 1987; Moore et al., 1992).

In previous studies we have shown that GH therapy in a regular substitution dosage leads to evident catch up growth in most children with ISS (Wit et al., 1989b) and that doubling the dosage in the poor responders causes a similar growth response (Wit et al., 1989a; 1990). We now report on the long-term effects of GH on statural growth, bone maturation was accelerated in the ISS and GHD groups. HSDS for bone age and predicted adult height did not change in either group. Final height in 12 children of the ISS group was $-2.6 \pm 1.0$ SDS. In the untreated controls final height was similar. A low integrated GH concentration over 24 hours, a low GH peak to provocative stimuli, and minimal initial BA delay predicted a favourable outcome.

CONCLUSION rhGH treatment in this group of children with idiopathic short stature did not increase average final height. Part of the heterogeneity of the response can be attributed to the variation in endogenous GH secretion and initial bone age delay.

Summary

BACKGROUND AND OBJECTIVE Growth hormone treatment in children with idiopathic short stature (ISS) leads to growth acceleration in the first years, but the effect on final height is still poorly documented. We therefore studied the long-term effect of GH therapy in children with idiopathic short stature.

DESIGN We have treated 27 prepubertal children with ISS with recombinant human GH (rhGH) in an initial dosage of 2 IU/m² body surface/day subcutaneously, which was doubled either after the first year if the height velocity increment was less than 2 cm/year, or thereafter if height velocity fell below the P50 for bone age. Growth and bone maturation of the treatment group (ISS group, n = 21) were compared to those of an untreated control group with ISS (ISS controls, n = 27) and of a group of rhGH treated children with isolated GH deficiency (GHD group, n = 7).

RESULTS In 9 patients of the ISS group still on treatment, height standard deviation score (HSDS) for chronological age increased from $-3.8 \pm 0.7$ to $-2.3 \pm 0.9$ (mean ± standard deviation) over 6 years, while in matched ISS controls HSDS for age did not change. HSDS for age in the GHD group increased from $-3.9 \pm 0.6$ to $-1.8 \pm 0.7$ after 4 years, significantly more than the ISS group. Bone

Correspondence: Professor Dr J. M. Wit, Department of Paediatrics, Academic Hospital Leiden, PO Box 9600, 2300 RC Leiden, The Netherlands.

© 1995 Blackwell Science Ltd
maturation, pubertal development and final height in these children. We tested the hypothesis that GH leads to a significant growth response in comparison to untreated controls, but that this response is less than that observed in children with 'classic' isolated GH deficiency. We further evaluated the predictive value of clinical and biochemical variables for the effect of GH therapy on final height.

Methods

Patient population

Thirty prepubertal children (21 boys and 9 girls) with ISS were selected from five Dutch paediatric endocrine centres. To participate in this study the children had to fulfil the following criteria: age above 6 years, bone age according to Tanner and Whitehouse method II (20 bones) less than 10 years in girls or 11 years in boys, HSDS for age less than −2.5 compared to Dutch cross-sectional standards (Roede & Van Wieringen, 1985), height velocity for bone age below the 25th percentile (Tanner et al., 1966) and plasma GH levels >7.5 μg/l (15mU/l) in at least one standard provocation test. Organic causes of growth failure were excluded. The study was approved by the hospital ethical committees of the participating centres and informed consent was obtained from all parents and patients.

Initially the children were randomly assigned to a treatment group or to a prospective control group. During the first year of the study, a significant increase in height velocity occurred in the treatment group (Wit et al., 1989b), and subsequently therapy was also offered to the control group for ethical reasons. Three children decided to remain without rhGH therapy, one of whom later participated in another study, resulting in a treatment group of 27 children. During the follow-up period, 6 of these 27 patients dropped out of the study. One child stopped after 6 months because she had a poor growth response in the presence of a high titre of antibodies; the remaining five children stopped therapy after 9 months and 1, 2, 3, and 4 years of treatment due to poor compliance. The patients who dropped out of the study did not differ from the patients who remained on therapy regarding age, HSDS for age or bone age at the start of therapy, or for response to rhGH therapy in terms of height velocity and the change in HSDS for age. Hence, the final number of children who received long-term rhGH was reduced to 21 (14 boys, 7 girls). Four of these children were classified (Ranke, 1991) as familial short stature, 5 as constitutional delay, 6 as a combination of both, 4 (one of whom had stigmata suggestive of Silver-Russell syndrome) as persistent short stature after intrauterine growth retardation and 2 as unspecified ISS. At present, 9 of these children are still undergoing treatment (ISS group 1, n = 9, 7 boys), whereas 12 children have reached final height (ISS-group 2, n = 12, 7 boys). Relevant data on these groups, as well as on control groups which are described below, are shown in Tables 1 and 2.

Control groups

As the original prospective control group was reduced to 2 children, we retrospectively collected growth data for untreated children with ISS. From the medical records of all Dutch paediatric endocrinology centres, 27 children were recruited who fulfilled the same inclusion criteria as the study group and for whom individual growth data over 6 years as well as data on final height could be obtained.

Table 1 Data before and during GH treatment of ISS patients still on GH therapy in comparison with matched controls and GHD patients

<table>
<thead>
<tr>
<th></th>
<th>ISS Group 1 (9(7/2))</th>
<th>Matched ISS controls (9(7/2))</th>
<th>GHD Group (7(3/4))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start 4 years GH 6 years GH</td>
<td>Start 4 years GH 6 years GH</td>
<td>Start 4 years GH</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.2±1.6 13.2±1.5 15.2±1.6</td>
<td>9.1±1.7 13.1±1.7 15.1±1.7</td>
<td>8.2±2.0 12.2±2.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>115.6±6.9 141.5±7.6 152.3±10.1</td>
<td>118.4±8.7 134.2±8.1 145.1±8.8</td>
<td>110.2±9.5 140.9±11.2</td>
</tr>
<tr>
<td>Height (SDS for age)</td>
<td>-3.8±0.7 -2.5±0.7** -2.3±0.9**</td>
<td>-3.2±0.3 -3.4±0.6 -3.3±0.6</td>
<td>-3.9±0.6 -1.8±0.7*</td>
</tr>
<tr>
<td>Bone age (G-P)†</td>
<td>6.4±1.6 11.8±1.0 13.4±0.9</td>
<td>n.a. n.a. n.a.</td>
<td>5.8±2.4 10.8±2.0</td>
</tr>
<tr>
<td>Height (SDS for BA-G-P)‡</td>
<td>-1.0±1.7 -1.5±1.1 -1.1±1.2</td>
<td>n.a. n.a. n.a.</td>
<td>-1.1±1.3 -0.9±0.6</td>
</tr>
<tr>
<td>Prediction (SDS)†‡</td>
<td>-2.4±1.7 -2.1±1.2 -1.8±1.6</td>
<td>n.a. n.a. n.a.</td>
<td>n.a.§ -1.7±0.7</td>
</tr>
</tbody>
</table>

† n = 6 in the GHD group because the bone age after 4 years of GH therapy is missing in 1 patient.
‡ n = 8 in the ISS group because the bone age at start was too low for prediction in 1 case.
§ Not available; in 5 cases the bone age at start was too low for prediction.
* P < 0.05 compared to start.
** P < 0.01 compared to start.
n.a., Not available.

© 1995 Blackwell Science Ltd, Clinical Endocrinology, 42, 4
Long-term GH therapy in idiopathic short stature

Table 2 Data of patients who reached final height.

<table>
<thead>
<tr>
<th></th>
<th>ISS Group 2</th>
<th>ISS controls</th>
<th>ISS BA controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (Male/female)</td>
<td>12 (7/5)</td>
<td>27 (16/11)</td>
<td>9 (5/4)</td>
</tr>
<tr>
<td>Start</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.2 ± 1.5</td>
<td>10.5 ± 1.2</td>
<td>10.1 ± 0.9</td>
</tr>
<tr>
<td>Bone age (G-P)</td>
<td>8.4 ± 1.3</td>
<td>n.a.</td>
<td>7.6 ± 1.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>124.6 ± 7.9</td>
<td>125.5 ± 5.4</td>
<td>123.4 ± 4.5</td>
</tr>
<tr>
<td>Height (SDS for age)</td>
<td>-3.5 ± 0.8</td>
<td>-3.0 ± 0.4</td>
<td>-3.1 ± 0.3</td>
</tr>
<tr>
<td>Height (SDS for bone age G-P)</td>
<td>-1.5 ± 0.6</td>
<td>n.a.</td>
<td>-0.8 ± 1.4</td>
</tr>
<tr>
<td>Prediction (cm)</td>
<td>158.8 ± 7.9</td>
<td>n.a.</td>
<td>160.2 ± 6.7*</td>
</tr>
<tr>
<td>Prediction (SDS)</td>
<td>-2.7 ± 0.6</td>
<td>n.a.</td>
<td>-2.4 ± 0.7*</td>
</tr>
</tbody>
</table>

Final measurement

|                          |              |              |                |
| Age (year)               | 16.9 ± 1.3   | 22.0 ± 3.1   | 22.3 ± 2.6     |
| Height (cm)              | 159.2 ± 8.0  | 160.6 ± 6.6  | 159.0 ± 6.9    |
| Height (SDS for age)     | -2.4 ± 0.9   | -2.4 ± 0.7   | -2.6 ± 0.9     |
| Height (SDS for adults)  | -2.6 ± 1.0   | n.a.         | -2.0 ± 3.5*    |
| Height—prediction at 0 (cm) | 0.4 ± 0.5  | n.a.         |                |
| Height—target height (cm) | -8.7 ± 6.5  | -8.9 ± 4.9   | -10.2 ± 3.5    |

* n = 7, for two patients the bone age at start was too low for prediction. n.a., Not available.

(ISS controls). Four of these patients were classified (Ranke, 1991) as familial short stature, 18 as constitutional delay and 5 as a combination of both. They had not undergone any treatment known to influence adult height. The start of the observation period for these children was defined as the visit to the hospital when they had an age close to the mean age at start of the study population. In 9 subjects it was possible to have a reassessment by the principal investigator (JMW) of an X-ray of the left hand made at the start of the observation period.

A second group used for the analysis was formed by patients with isolated GHD who were selected retrospectively from the Dutch nationwide database on GH treated individuals. The GHD patients had to fulfil the same inclusion criteria as the study group with exception of the maximum plasma GH level, which had to be below 7.5 µg/l in all performed standard provocation tests. Moreover, GH therapy had to be administered at a frequency of 6 or 7 injections/week and a minimum of 4 years of follow-up after start of GH treatment had to be available. Of the 89 patients with isolated GHD in the database only 7 patients fulfilled all requirements (GHD group, n = 7). The GH dosage used in the GHD-group over 4 years was 14.8 ± 4.1 IU/m²/week (mean ± SD).

Treatment protocol

During the first 2 years of the study treatment consisted of biosynthetic methionyl human GH (Somatonorm, Kabi Pharmacia, Sweden) and from the third year onwards this was replaced by authentic recombinant human GH (Genotropin, Pharmacia). In all ISS patients treated with rhGH the starting dosage was 2 IU/m² body surface/day administered 7 times a week subcutaneously. The individual results of therapy were evaluated yearly and children were categorized as responders or non-responders. After the first year of the study a non-responder was defined by a height velocity increment of less than 2 cm/year. From the second year onwards a child was labelled as a non-responder if the height velocity dropped below the 50th percentile for bone age. In the non-responders, the dosage was doubled to 4 IU/m² body surface daily.

Evaluation

At baseline, a 24-hour serum GH profile and the plasma IGF-I concentration was determined in the initial treatment group. The GH profile was obtained by a CORMED automatic exfusion pump with 20 minutes sampling and the integrated concentration of serum GH was calculated. The assays of serum GH and plasma IGF-I have been described earlier (Wit et al., 1989b). Height was measured every 3 months at the same time of the day using a Harpenden stadiometer. The mean of 4 measurements was used for analysis. Pubertal stages were scored according to the Tanner (1953) classification and compared with longitudinal British references (Marshall & Tanner, 1969; 1970). Bone age determinations were performed by the same
investigator using the method of Greulich and Pyle (1959) as well as the Tanner and Whitehouse method II (20 bones) (Tanner et al., 1983). Height was expressed as HSDS for age (Roede & Van Wieringen, 1985) and bone age. Height velocity was calculated over full years as SDS for bone age (Tanner et al., 1966), on which basis the dosage was or was not adapted. Height predictions were calculated by the method of Bayley and Pinneau (1952). Heights of father and mother were measured and target height was calculated as the sex-corrected mid parental height plus 3 cm, to account for the average secular trend.

We also investigated the predictive value, with respect to long-term response to rhGH therapy, of certain baseline parameters and of the height velocity increment during the first year of therapy. In this analysis HSDS for age, height velocity SDS for age, bone age delay, 24-hour integrated concentration of GH, maximum GH concentration during provocative test, plasma IGF concentration and height velocity increment during the first year of therapy were considered as independent variables while the difference between final height (ISS group 1) or predicted adult height after 6 or 7 years of rhGH therapy (ISS group 2) and the predicted adult height at start of therapy were used as measures of the response to rhGH treatment (dependent variable).

**Statistical analysis**

Results are expressed as mean ± standard deviation (SD) unless indicated otherwise. Paired t-tests or repeated-measures analysis of variance and, in case of non-normality, Wilcoxon signed rank or Friedman statistic tests, were performed to assess differences within the groups. To test differences between the groups unpaired t-tests or analysis of variance and, in case of non-normality, Wilcoxon signed rank or Kruskal-Wallis tests were used. The correlations between various parameters were calculated by univariate linear regression analysis and expressed by Pearson’s correlation coefficient. Figures present mean ± 1 standard deviation.

**Results**

Over the first year of rhGH treatment, 16 out of the 21 children in the ISS treatment group (76%) showed a height velocity increment of more than 2 cm/year on a dosage of 2 IU/m² daily. Four of them kept a height velocity above the mean for bone age during the complete treatment period, and continued on the initial dosage of 2 IU/m² daily until they reached final height. The remaining 17 children were all labelled as non-responders at variable intervals (1–5 years) after the start of rhGH and the dosage was doubled. At present 9 of the 21 treated patients are still on rhGH therapy (ISS group 1), all on a dose of 4 IU/m² b.s. daily, whereas 12 children have reached final height (ISS group 2). No clinical side-effects have been reported. All laboratory parameters remained normal during therapy.

**Growth in patients still on rhGH therapy**

In order to evaluate the efficacy of rhGH treatment in children with ISS who are still growing, we compared growth data of the ISS group 1 with those of a matched subsample of the untreated controls (matched ISS controls, n = 9) and with the GHD-group. The matching procedure, based on sex, age and HSDS for age at the start of the observation period, was performed because the HSDS for age at start was significantly higher in the complete cohort of ISS controls than in the ISS treatment group. At the start of the study there were no differences between the ISS group 1, the matched ISS controls and the GHD group regarding age and HSDS for age. Moreover, no differences between the ISS group 1 and the GHD group were present regarding bone age or HSDS for bone age (Table 1). A comparison of initial final height predictions with the Bayley-Pinneau method was not possible because in 5 patients from the GHD group the bone age at start was too young.

**Height SDS for chronological age (Table 1, Fig. 1a).** In ISS group 1 the HSDS for age rose from −3.8 ± 0.7 at start of therapy to −2.5 ± 0.7 (P < 0.01) and −2.3 ± 0.9 (P < 0.01) after 4 and 6 years, respectively. In the matched ISS control...
patients, HSDS for age did not change during 6 years of follow-up: at the 'start' HSDS for age was \(-3.2 \pm 0.3\), after 4 years it was \(-3.4 \pm 0.6\), and after 6 years \(-3.3 \pm 0.6\). The GHD group, for which data are available over a 4-year period of rhGH therapy, showed a significant increase in HSDS for age from \(-3.9 \pm 0.6\) to \(-1.8 \pm 0.7\) (\(P < 0.02\)). After 4 and 6 years of follow-up the HSDS for age in ISS group 1 was significantly higher than in the matched ISS controls (\(P < 0.002\)). The HSDS for age of the GHD group after 4 years of treatment was also significantly higher than in the ISS controls (\(P < 0.002\)). Although the absolute values of HSDS for age after 4 years of rhGH treatment were not different between the ISS group 1 and the GHD patients, the increment of HSDS for age was significantly larger in the GHD group than in the rhGH treated ISS group 1 (\(2.0 \pm 0.4\) vs \(1.3 \pm 0.6\), \(P < 0.02\)).

**Bone age development.** During the first 4 years of rhGH therapy the mean bone age advancement according to Greulich and Pyle in ISS group 1 was comparable to that in the GHD group: \(5.4 \pm 0.8\) years and \(5.0 \pm 0.8\) years, respectively. In both groups the increment in bone age exceeded the increment in age during this period (\(P < 0.05\)). In ISS group 1 the mean bone age increment over 6 years of treatment was \(7.0 \pm 1.3\) years.

**Height SDS for bone age (Fig. 1b).** In both ISS group 1 and the GHD group, HSDS for bone age showed little change. HSDS for bone age after 4 years of rhGH did not differ between the groups, and its change over 4 years was \(-0.5 \pm 1.0\) in the ISS group and \(+0.2 \pm 1.0\) in the GHD group (NS).

**Predicted adult height (Table 1).** In ISS group 1 predicted adult height SDS increased from \(-2.4 \pm 1.7\) to \(-1.8 \pm 1.6\) after 6 years of rhGH therapy (NS). The increment in predicted adult height SDS was \(0.6 \pm 1.1\) (NS). As explained earlier, no data on predicted adult height changes could be calculated for the GHD group.

**Data on final height**

In order to study final height results of rhGH therapy in ISS we compared the data of the treated ISS subjects who have reached final height (ISS group 2) with those of a second subsample of the retrospectively selected cohort of untreated children with ISS in whom reassessment of bone age could be performed (ISS bone age controls, \(n = 9\)). The results are shown in Table 2. ISS bone age controls did not differ from the complete untreated control group regarding age, height, and HSDS for age at start of the observation period. The mean final height SDS in all groups were similar and higher than the initial HSDS. However, final height was close to the initial Bayley–Pinneau predictions, while HSDS for BA overpredicted final height in the treatment and control group with a mean \(\pm\) SD of \(1.1 \pm 0.8\) and \(1.8 \pm 1.1\) SDS, respectively. The final height of ISS group 2 was \(8.7 \pm 6.5\) cm below the target height (\(P < 0.005\)), compared to \(10.2 \pm 3.5\) cm in the ISS bone age control group (\(P < 0.0001\)). A comparison within ISS group 2 of the patients who always received a dosage 2 IU/m2 b.s. daily and those in whom the dosage was doubled, revealed no significant differences with respect to final height, final height minus target height, final height minus predicted adult height at start of therapy, HSDS for age at stop and HSDS for adults (data not shown). A similar comparison between boys and girls also revealed no differences.

**Pubertal development**

All 21 children from both ISS groups entered puberty during the treatment period, and 18 had reached at least pubertal stage 4 at the moment of analysis. The chronological age at onset of puberty, which is defined as Tanner stage G2/B2, was \(13.7 \pm 1.2\) years in boys and \(11.7 \pm 0.8\) years in girls, whereas the mean British references are \(11.6 \pm 1.1\) years and \(11.2 \pm 1.1\) years, respectively (Marshall & Tanner, 1969; Marshall & Tanner, 1970; 1969). The bone age according to Greulich and Pyle at start of puberty was \(11.5 \pm 0.9\) in boys and \(10.3 \pm 0.3\) in girls. At
Factors predicting the outcome of rhGH therapy

Table 3 shows the results of univariate linear regression analysis between some initial clinical and biochemical parameters and the final response to rhGH therapy, defined as the difference between final height (ISS group 2) or the predicted adult height after 6 or 7 years of rhGH treatment (ISS group 1) and the initial predicted adult height. The response to rhGH treatment was significantly negatively related to the bone age delay at start of therapy ($r = -0.52; P = 0.02$), to the integrated concentration of GH ($r = -0.61; P = 0.02$), and to the maximum GH peak during a provocation test ($r = -0.58; P < 0.02$). A stepwise multiple regression analysis showed that bone age delay at start of therapy and integrated concentration of GH were the parameters with the highest predictive value, and resulted in the following equation:

\[
\text{height gain} = -4.48(\text{SE 1.00}) \times \text{BA delay at start} - 0.95(\text{SE 0.30}) \times \text{ICGH} + 20.65(\text{SE 3.17})
\]

No relation was found with the initial plasma concentration of IGF-I, HSDS for age, height velocity SDS for age, or with the height velocity increment during the first year of treatment. Bone age delay was positively correlated with the ratio of bone age advance over age during 4 years of GH therapy ($r = 0.50; P = 0.02$), but not with integrated concentration of GH ($r = 0.20; \text{NS}$). Similar correlations were found if only the children in whom final heights were available were included.

Discussion

The present study, as well as previous papers (Hopwood et al., 1993; Hindmarsh & Brook, 1987; Moore et al., 1992; Wit et al., 1989a,b; 1990), demonstrates that GH therapy in a daily dose of 1–2 times the substitution dose leads to increased growth velocity over several years in children with ISS, resulting in a HSDS increment of 1.5, provided that the dosage is adapted to the individual sensitivity. The average response, however, was less than the response of children with ‘classic’ isolated GHD to a substitution dosage (approximately 2 SD over 4 years) and the mean height remained below the 3rd percentile.

The response to GH therapy in ISS was, besides being lower than in GH deficient children, also heterogeneous. In fact, 75% of our patients showed a significant acceleration in height velocity during the first year of treatment with a regular substitution dose of rhGH, whereas in the others a higher dose was needed to obtain a significant increment. In the following years, the GH dosage had to be doubled in most of our patients in order to maintain the height velocity above the mean for bone age. Only in 4 patients, of whom 3 had a low integrated concentration of GH, was the regular GH dosage sufficient to maintain growth velocity above the average for bone age until final height.

These results, in combination with the wide variation in endogenous GH secretion in our patients (Wit et al., 1989b), are in line with the earlier observations that children with ISS differ in terms of GH secretion and GH sensitivity: some children can be classified as suffering ‘GH neurosecretory dysfunction’ (Bercu et al., 1986; Spiliotis et al., 1984), while in others a relative insensitivity for GH is suggested by relatively low levels of GH-binding protein (Fontoura et al., 1992), which may reflect the cellular GH receptor status (Daughaday et al., 1987) in such patients.

In contrast to the increase in HSDS for age, GH therapy did not increase HSDS for bone age or predicted adult height in children with ISS and GHD, due to the accelerated bone maturation, a finding also reported by other investigators (Hopwood et al., 1993; Tanaka et al., 1993). This may be partly caused by the shorter duration of
puberty as observed in the GH treated boys, which is in line with observations in GH deficient children (Darendeliler et al., 1990). However, the fact that this acceleration of bone maturation also occurs in girls with Turner’s syndrome treated with higher than replacement doses of rhGH (Massa et al., 1993; Rongen-Westerlaken et al., 1992) suggests that it is at least in part caused by a direct effect of GH or insulin-like growth factors on the developing growth cartilage, and not only by sex steroids. Studies evaluating the effect of delaying puberty in ISS subjects during rhGH treatment with GnRH-agonists, are needed to answer the question whether pubertal development substantially interferes with the growth promoting effect of GH.

So far, limited information is available on final height of children with ISS treated with GH. Our results show that, although final height SDS for age is about 1 SD higher than the initial HSDS, it is still situated 2·5 SD below the population's mean and 9 cm below target height, similarly to untreated controls. These findings suggest that the average result of 6 or more years daily rhGH injections is about 0·4 SD, which is 2·4 cm. These results are not necessarily in conflict with the results of a study (Zadik et al., 1992b) showing a positive effect of GH on final height in 17 peripubertal boys with ISS and a subnormal integrated concentration of GH, as in our study also children with a low integrated concentration of GH did better than the others. Our data are in line with those of a recent collaborative study on children with variable endogenous GH secretion (Guyda, 1994).

In the children with ISS who did not undergo GH treatment, final height was very close to the prediction at the start of the observation period, but significantly below the target height and below the initial HSDS for bone age, which is consistent with earlier reports (Brämswig et al., 1990; Crowne et al., 1990). This means that for a group analysis predicted adult height can be used for evaluating the effect of GH therapy, although on an individual basis there is still a substantial error.

We have previously reported that indicators of endogenous GH secretion did not predict the first year response to GH treatment (Wit et al., 1989b). In contrast to this finding, our present analysis shows that the integrated concentration of GH and the GH response to secretagogues are significantly negatively correlated to the long-term effect of rhGH treatment: the lower the integrated concentration of GH and stimulated GH secretion, the better the effect of GH treatment on final height. This is in line with the observations of Zadik et al. (1992a) reporting that the benefit from GH therapy in children with a normal growth velocity and a normal integrated concentration of GH is poor, whereas marked growth acceleration was noted in children with a low growth velocity and a low 24-hour integrated concentration of GH. It is also compatible with the general assumption that the response to GH therapy is better in GH deficiency than in other short children.

A surprising finding was that the bone age delay, which would be suspected to correlate positively with the degree of GH insufficiency and therefore with the gain in final height, was negatively related to the final outcome. This is probably caused by a relatively large bone age advance in children with a large initial bone age delay, thereby limiting the effect on final height. Height velocity before or during the first year of treatment had no predictive value, suggesting that short-term results do not reflect long-term results of GH treatment.

In conclusion, GH treatment induces a significant increase of height standard deviation score for chronological age during treatment in idiopathic short stature, but average final height does not improve due to advanced bone maturation. In children with classic isolated GH deficiency the growth response is better, but also associated with an advancement of bone age. There is a large interindividual variation in the response to GH treatment and a 24-hour integrated concentration GH can to some extent discriminate between responders and non-responders, while a large bone age delay is a negative predictor. Assuming that a taller final height is the main response parameter, rather than a temporary growth acceleration during childhood and adolescence, GH treatment is not indicated in short children without clear evidence for GH deficiency. Further refinement of the diagnosis of GH secretion and GH responsiveness is needed for a better selection of patients eligible for GH therapy.

Acknowledgements

This work was supported by a grant from Kabi Pharmacia Peptide Hormones.

References


