Combined Use of Growth Hormone and Gonadotropin-releasing Hormone Analogues: The National Cooperative Growth Study Experience

Brenda Kohn, MD*; Joanne R. Julius, MS‡; and Sandra L. Blethen, MD, PhD‡

ABSTRACT. Gonadotropin-releasing hormone analogues (GnRHa) are used to treat central precocious puberty. They also are used to delay puberty in short children with a prognosis for impaired adult height. In both cases, growth hormone (GH) treatment is sometimes added. To determine how North American pediatric endocrinologists are using the combination of GH and GnRHa, we searched the National Cooperative Growth Study (NCGS) database and identified 509 patients who were treated with both. Among them were 139 patients with a diagnosis of precocious puberty. Most of these (82%) also had GH deficiency (GHD). Of the 370 patients who did not have precocious puberty, 71% had GHD. There were 200 patients with precocious puberty who were treated with GH but not with GnRHa. The children who were given GH alone (77% of whom had GHD) were much younger than the children who were given both GH and GnRHa (5.7 ± 2.9 years for those who were not treated with GnRHa vs 9.1 ± 2.7 years for those who were). Data on both predicted adult height before GH treatment and near-adult height were available for 141 of the patients who were given both GH and GnRHa. There was a statistically significant increase in near-adult height over pre-GH predicted adult height in girls with precocious puberty (5.4 ± 4.3 cm) and without precocious puberty (3.0 ± 6.1 cm). There was no statistically significant gain in height for boys who did not have precocious puberty (1.3 ± 6.8 cm). There were too few boys with precocious puberty (n = 7) to enable meaningful conclusions. In a multiple regression analysis of data on girls who did not have precocious puberty, duration of GH treatment was the most important variable predictive of height gain. Pediatrics 1999;104:1014–1017; gonadotropin-releasing hormone, growth hormone, precocious puberty.
idiotic growth hormone deficiency, organic growth deficiency, idiopathic short stature.

**ABBREVIATIONS.** GnRHa, gonadotropin-releasing hormone analogue(s); GH, growth hormone; GHD, growth hormone deficiency; NCGS, National Cooperative Growth Study; IGHD, idiopathic growth hormone deficiency; OGHD, organic growth hormone deficiency; ISS, idiopathic short stature.

Gonadotropin-releasing hormone analogues (GnRHa) are indicated for the treatment of central precocious puberty. They slow or stop the development of secondary sexual characteristics, bone age progression, and rapid growth. By slowing skeletal maturation, they have the potential to extend the time available for prepubertal growth. In many cases, however, the growth rates during GnRHa therapy are less than those observed in normal prepubertal children. Because increased secretion of growth hormone (GH) plays an important role in the pubertal growth spurt, it has been suggested that a combination of GH and GnRHa might lead to a greater adult height because exogenous GH replaces the secretion of endogenous GH that is stimulated by estrogen. The basis for this suggestion is reviewed elsewhere in this supplement issue.

Both GH deficiency (GHD) and precocious puberty develop in many children who undergo cranial irradiation. Clinicians also have used a combination of GH and GnRHa in children with severe short stature who begin puberty with a significant height deficit.

We used the National Cooperative Growth Study (NCGS), a large database of children treated with GH, to determine how North American pediatric endocrinologists use combined GnRHa and GH therapy. We also report some preliminary data on the effect of combined treatment on adult height.

**SUBJECTS AND METHODS**

**Patients**

The NCGS is an observational registry of children treated with recombinant GH products manufactured by Genentech, Inc (South San Francisco, CA). Methods of patient enrollment and data collection have been described elsewhere. We identified 509 children who had been treated with a GnRHa at some time during their treatment with GH. They were subdivided into those who had precocious puberty and those who did not. A child was considered to have precocious puberty if this diagnosis was indicated on the enrollment form or if breast development (girls) or testicular size (boys) was recorded as Tanner stage 2 or greater on any form before the child was 8 years old (girls) or 9 years old (boys). Two comparison groups of patients, one with precocious puberty who had not been treated with GnRHa and a core group who did not have precocious puberty and had not been treated with GnRHa, were also identified.

Children were categorized as having idiopathic GH deficiency (IGHD), organic GH deficiency (OGHD), or idiopathic short stature (ISS) based on data on the enrollment forms. A child was considered to have GHD if the maximum stimulated GH level was $\geq 10 \mu g/L$ and no other causes of growth failure were given on the enrollment form.

To study the effects of GnRHa treatment on adult height, we identified a group of patients who were naïve to GH when they were enrolled in the NCGS and who had their bone age measured no more than 180 days before or 90 days after the start of GH treatment. Patients had to have undergone at least 6 months of GH treatment and have a near-adult height measurement available. Near-adult height was defined as a height measured after a chronologic age or bone age of 14 years (girls) or 16 years (boys). There were 141 children who met these criteria.

**Statistics**

Descriptive statistics were generated for the following groups: all patients treated with GnRHa; patients with IGHD, OGHD, or ISS not treated with GnRHa (core group); patients with precocious puberty treated with GnRHa; and patients with precocious puberty not treated with GnRHa. Categoric variables, such as sex; cause of short stature (IGHD, OGHD, or ISS); and pubertal stage were summarized by frequency and percentage. Continuous variables, such as age and height, were reported as mean and standard deviation.

Comparisons of the categoric variables used $\chi^2$ tests. Comparisons of the continuous variables used Student’s $t$ test. Increases in adult height were calculated by comparing the Bayley-Pinneau predicted height at the start of GH treatment with the near-adult height by using the paired $t$ test. The variables that had an impact on increases in adult height were assessed by using linear regression analysis. Because of sample size limitations, regression analysis was restricted to girls who did not have precocious puberty.

**RESULTS**

**Patient Characteristics**

Characteristics of patients with precocious puberty who were given GnRHa; other patients who were given GnRHa; patients with precocious puberty who were not given GnRHa; and the core group of patients with IGHD, OGHD, or ISS who were neither given GnRHa nor had precocious puberty are shown in Table 1. The majority of patients given GnRHa in conjunction with GH had GHD (82% of those with precocious puberty and 71% of those with normal puberty). However, only 27% had a diagnosis of precocious puberty. Compared with children in the core group, children who were given GnRHa were more likely to be girls, to have OGHD ($P = .001$), and to have been in puberty ($P = .001$) when they began GH treatment.

**Children With Precocious Puberty**

There were clear differences between the children with precocious puberty who were treated with GnRHa and those who were not (Table 1). The children with precocious puberty who were given GnRHa were older and were more likely to be girls and to have OGHD. There was no bone age delay in most of the children who were given GnRHa.

**Adult Height in Patients Treated With GnRHa in Addition to GH**

Because of the marked differences between the children who were treated with GnRHa and those who were not, direct outcome comparisons of adult height would not have been meaningful. Furthermore, very few of the untreated children with precocious puberty had attained near-adult height. For these reasons, we confined our analysis of the effect of combined GH and GnRHa therapy on adult height to patients for whom
an enrollment bone age (and thus an adult height predicted by the Bayley-Pinneau method) was available. Patients with near-adult height data were subdivided by sex and whether they had a diagnosis of precocious puberty. Characteristics of the patients in the near-adult height analysis are shown in Table 2. Girls with precocious puberty were younger chronologically but had more advanced skeletal maturation. Although they were taller when they started GH, their pre-GH predicted height was the lowest.

**Height Gain**

The characteristics of the patients when they reached near-adult height are shown in Table 3. It should be noted that the last bone age was not necessarily taken at the same time as the last height measurement. As shown in Fig 1, the girls with precocious puberty had a highly significant gain in near-adult height (5.4 ± 4.3 cm; \( P < .001 \)), as did the girls with normal pubertal onset (3.0 ± 6.1 cm; \( P < .001 \)). There was no statistically significant increase in near-adult height over pre-GH predicted height in the boys with normal puberty (1.3 ± 6.8 cm).

**Factors Influencing Outcome**

Multiple regression analysis was used to explore the variables associated with a greater height gain in the girls with normal pubertal onset. The duration of GH treatment was the most important predictor of the outcome (\( P = .0001 \)). The pre-GH bone age was the second most important outcome predictor, but its relation to height gain was complex. Bone age was highly nega-

### TABLE 1. Characteristics of NCGS Patients

<table>
<thead>
<tr>
<th>Patient Group (n)</th>
<th>Precocious Puberty + GnRHa (139)</th>
<th>Normal Puberty + GnRHa (370)</th>
<th>Precocious Puberty, No GnRHa (200)</th>
<th>Core Patients With IGHD, OGHHD, or ISS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at NCGS enrollment (y)</td>
<td>9.1 ± 2.7</td>
<td>10.9 ± 2.9</td>
<td>5.7 ± 2.9</td>
<td>10.2 ± 4.1</td>
</tr>
<tr>
<td>Height SD score at enrollment</td>
<td>−1.5 ± 1.7</td>
<td>−2.7 ± 1.3</td>
<td>−2.6 ± 1.3</td>
<td>−2.7 ± 1.0</td>
</tr>
<tr>
<td>Midparental height SDS</td>
<td>−0.4 ± 0.8 (101)*</td>
<td>−0.6 ± 0.9 (303)*</td>
<td>−0.3 ± 1.0 (165)*</td>
<td>−0.5 ± 0.8 (15,935)*</td>
</tr>
<tr>
<td>Bone age (y)</td>
<td>9.9 ± 3.5 (73)*</td>
<td>9.8 ± 3.3 (239)*</td>
<td>4.4 ± 3.0 (113)*</td>
<td>8.4 ± 3.8 (11,899)*</td>
</tr>
<tr>
<td>Pubertal status at enrollment (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanner stage 1</td>
<td>24</td>
<td>51</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>Tanner stage 2</td>
<td>30</td>
<td>27</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Tanner stage 3</td>
<td>33</td>
<td>13</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Tanner stage 4 or 5</td>
<td>14</td>
<td>9</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>31/69</td>
<td>51/49</td>
<td>66/34</td>
<td>73/27</td>
</tr>
<tr>
<td>Cause of growth failure (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGHD</td>
<td>29</td>
<td>35</td>
<td>58</td>
<td>57</td>
</tr>
<tr>
<td>OGHDD</td>
<td>53</td>
<td>36</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>ISS</td>
<td>18</td>
<td>29</td>
<td>24</td>
<td>26</td>
</tr>
</tbody>
</table>

* Values in parentheses are number of patients when less than the total.

### TABLE 2. Characteristics of Patients Treated With GH and GnRHa With Near-adult Heights

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment (y)</td>
<td>11.0 ± 1.6</td>
<td>11.9 ± 2.0</td>
<td>13.5 ± 2.4</td>
</tr>
<tr>
<td>Bone age at enrollment (y)</td>
<td>12.3 ± 1.7</td>
<td>10.9 ± 2.2</td>
<td>11.8 ± 2.5</td>
</tr>
<tr>
<td>Height SDS</td>
<td>−1.8 ± 1.4</td>
<td>−2.8 ± 1.2</td>
<td>−2.9 ± 0.9</td>
</tr>
<tr>
<td>Pre-GH predicted height (cm)</td>
<td>143 ± 5</td>
<td>146 ± 7</td>
<td>162 ± 7</td>
</tr>
<tr>
<td>Midparental target height (cm)</td>
<td>162 ± 4 (13)*</td>
<td>160 ± 4 (51)*</td>
<td>173 ± 6 (49)*</td>
</tr>
<tr>
<td>Cause of growth failure (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGHD (%)</td>
<td>33</td>
<td>32</td>
<td>46</td>
</tr>
<tr>
<td>OGHDD (%)</td>
<td>44</td>
<td>35</td>
<td>13</td>
</tr>
<tr>
<td>ISS (%)</td>
<td>22</td>
<td>32</td>
<td>41</td>
</tr>
<tr>
<td>Prepubertal at enrollment (%)</td>
<td>0</td>
<td>29</td>
<td>40</td>
</tr>
</tbody>
</table>

* Values in parentheses are number of patients when less than the total.

### TABLE 3. Patient Characteristics at Near-adult Height

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at near adult height (y)</td>
<td>14.3 ± 1.7</td>
<td>15.3 ± 1.8</td>
<td>17.4 ± 1.1</td>
</tr>
<tr>
<td>Last bone age (y)</td>
<td>13.4 ± 1.0</td>
<td>12.9 ± 1.6</td>
<td>14.7 ± 1.4</td>
</tr>
<tr>
<td>Near-adult height (cm)</td>
<td>148 ± 7</td>
<td>149 ± 7</td>
<td>163 ± 6</td>
</tr>
<tr>
<td>Height gain (cm)</td>
<td>5.4 ± 4.3*</td>
<td>3.0 ± 6.1*</td>
<td>1.3 ± 6.8</td>
</tr>
<tr>
<td>Duration of GH treatment (y)</td>
<td>2.9 ± 1.1</td>
<td>3.2 ± 1.7</td>
<td>3.7 ± 2.0</td>
</tr>
</tbody>
</table>

* \( P < .001 \).
tively correlated with the duration of GH treatment ($r = .65; P < .001$). This means that those with younger bone ages tended to have been treated longer, and those treated longer tended to have greater height gains. However, the regression coefficient for bone age is positive, which suggests that when duration of GH treatment is held constant (equal), those who have older bone ages tend to have greater height gains.

**DISCUSSION**

**Effect of GnRHa in Combination With GH on Adult Height**

In analyzing the effect of any intervention designed to increase adult height, it is important to remember that the apparent outcome will be affected by the methods used to predict adult height and the criteria used to define it.$^{11}$ The criteria used for this analysis were conservative, and some additional height gain might be expected.$^{11}$ The outcome of combined treatment in girls with precocious puberty was encouraging. All had some increase in height, and more than half had an increase of $>5$ cm. The response of girls with pubertal onset after 8 years of age also was statistically significant, but smaller. No significant increase in adult height after 8 years of age also was statistically significant. The outcome of combined treatment in girls with precocious puberty was encouraging. All had some increase in height, and more than half had an increase of $>5$ cm. The response of girls with pubertal onset after 8 years of age also was statistically significant, but smaller. No significant increase in adult height after 8 years of age also was statistically significant.

As Bourguignon$^{12}$ has pointed out, total pubertal height gain is a better index of the impact of puberty on growth than is the duration of puberty or the peak growth velocity during puberty. Adult height is the sum of the height at the start of puberty and the pubertal height gain. Pubertal growth decreases in amplitude with the age of onset of puberty, because the growth spurt is added to the childhood component of growth, which continues to decline with age.$^{13}$ Taken together, these findings suggest that the best way to increase adult height in children with GHD is to increase their prepubertal growth by beginning GH treatment early and using adequate doses of GH.$^{14}$

An NCGS study of adult height in children with isolated IGHD confirms this suggestion.$^{15}$ The pubertal height gain in children with GHD who are treated with GH is essentially the same as that which would be expected in children without GHD but with delayed puberty. Thus, there probably is a limit to the increase in adult height that can be gained by blocking normal pubertal development. Combined treatment with GH and GnRHa is most likely to benefit children with precocious puberty. Because the duration of treatment is such an important predictor of the outcome,$^{15}$ early diagnosis and intervention will give the best results.

**ACKNOWLEDGMENT**

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**REFERENCES**

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