
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,

From the *Division of Pediatric Endocrinology, Long Island College Hospital, Brooklyn, New York; and the ‡Department of Medical Affairs, Genentech, Inc, South San Francisco, California. Presented in part at the National Cooperative Growth Study Twelfth Annual Investigators Meeting; October 8–11, 1998; New Orleans, LA. Reprint requests to (S.L.B.) Genentech, Inc, Mail Stop 66, 1 DNA Way, South San Francisco, CA 94080-4990. Received for publication May 13, 1999; accepted Jun 22, 1999. PEDIATRICS (ISSN 0031 4005). Copyright © 1999 by the American Academy of Pediatrics.
Gonadotropin-releasing hormone analogues (GnRHa) are indicated for the treatment of central precocious puberty.1 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.2

Both GH deficiency (GHD) and precocious puberty develop in many children who undergo cranial irradiation.3,4 For these children, both GH and GnRHa may be necessary for the attainment of an adult height in the normal range.5,6 Clinicians also have used a combination of GH and GnRHa in children with severe short stature who begin puberty with a significant height deficit.7,8

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.

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, OGHD, 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>24/69</td>
<td>51/51</td>
<td>74/76</td>
<td>76/76</td>
</tr>
<tr>
<td>Tanner stage 2</td>
<td>30/70</td>
<td>27/27</td>
<td>18/18</td>
<td>16/16</td>
</tr>
<tr>
<td>Tanner stage 3</td>
<td>33/63</td>
<td>13/13</td>
<td>5/5</td>
<td>6/6</td>
</tr>
<tr>
<td>Tanner stage 4 or 5</td>
<td>14/28</td>
<td>9/9</td>
<td>4/4</td>
<td>2/2</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>29/55</td>
<td>35/58</td>
<td>58/57</td>
<td>57/57</td>
</tr>
<tr>
<td>OGHD</td>
<td>53/37</td>
<td>36/19</td>
<td>19/19</td>
<td>18/18</td>
</tr>
<tr>
<td>ISS</td>
<td>18/32</td>
<td>29/24</td>
<td>24/24</td>
<td>26/26</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>
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</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>33/67</td>
<td>32/32</td>
<td>46/46</td>
</tr>
<tr>
<td>OGHD (%)</td>
<td>44/56</td>
<td>35/35</td>
<td>13/13</td>
</tr>
<tr>
<td>ISS (%)</td>
<td>22/78</td>
<td>32/32</td>
<td>41/41</td>
</tr>
<tr>
<td>Prepubertal at enrollment (%)</td>
<td>0/18</td>
<td>29/29</td>
<td>40/40</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>
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<tr>
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</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>

* \( P < .001 \).
growth, which continues to decline with age.13 Taken
together, these findings suggest that the best way to
to increase adult height in children with GHD is to in-
crease their prepubertal growth by beginning GH treat-
ment early and using adequate doses of GH.14
An NCGS study of adult height in children with
isolated IGHD confirms this suggestion.15 The pu-
bertal 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 de-
layed puberty. Thus, there probably is a limit to the
increase in adult height that can be gained by block-
ing normal pubertal development. Combined treat-
ment with GH and GnRHa is most likely to benefit
children with precocious puberty. Because the dura-
tion of treatment is such an important predictor of
the outcome,15 early diagnosis and intervention will
give the best results.

ACKNOWLEDGMENT
This work was supported by an educational grant from Genen-
tech, Inc, South San Francisco, CA.

REFERENCES
acting agonist of gonadotropin-releasing hormone in the treatment of
precocious puberty. Endocr Res. 1986;7:24–33
2. Walvoord EC, Pescovitz OH. Combined use of growth hormone and
gonadotropin-releasing hormone analogues in precocious puberty: the-
3. Brauner R, Rappaport R. Precocious puberty secondary to cranial ir-
radiation for tumors distant from the hypothalamo-pituitary area. Horm
Res. 1985;22:78–82
4. Ogilvy-Stuart AL, Clayton PE, Shalet SM. Cranial irradiation and early
puberty. J Clin Endocrinol Metab. 1994;78:1282–1286
5. Cara JF, Kreiter ML, Rosenfield RL. Height prognosis of children with
true precocious puberty and growth hormone deficiency: effect of com-
bination therapy with gonadotropin releasing hormone agonist and
Combined treatment with gonadotropin-releasing hormone analog and
growth hormone in central precocious puberty. J Clin Endocrinol Metab.
1996;81:948–951
adolescent girls treated with gonadotropin-releasing hormone analog
and growth hormone. J Clin Endocrinol Metab. 1995;80:3596–3600
8. Tanaka T, Satoh M, Yasunaga T, Horikawa R, Tanae A, Hibi I. GH and
GnRH analog treatment in children who enter puberty at short stature.
J Pediatr Endocrinol Metab. 1997;10:623–628
the United States: demographic and diagnostic features of 2331 chil-
11. Frindik JP, Baptista J. Adult height in growth hormone deficiency:
historical perspective and examples from the National Cooperative
12. Bourguignon JP. Growth and timing of puberty: reciprocal effects. Horm
Res. 1991;36:131–135
using a mathematical model. II. From 3 to 21 years of age. Acta Paediatr
Suppl. 1987;337:12–29
14. MacGillivray MH, Blethen SL, Buchlis JG, Clopper RR, Sandberg DE,
Cowboy TA. Current dosing of growth hormone in children with
growth hormone deficiency: how physiologic? Pediatrics. 1998;102:
527–530. Supplement
15. August GP, Julius JR, Blethen SL. Adult height in children with growth
hormone deficiency who are treated with biosynthetic growth hormone:
the National Cooperative Growth Study experience. Pediatrics. 1998;102:
512–516. Supplement

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 meth-
ods used to predict adult height and the criteria used
to define it.11 The criteria used for this analysis were con-
servative, 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 signifi-
cant, but smaller. No significant increase in adult height
over pre-GH predicted height was seen in the boys
with normal onset of puberty.

Fig 1. Change in adult height over pre-GH predicted adult
height. The box indicates the 75th and 25th percentiles, the line in the box
indicates the median, and the solid square indicates the mean. The vertical
extensions indicate the 90th and 10th percentiles.

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.
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*Pediatrics* 1999:104:1014

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