Letrozole Significantly Improves Growth Potential in a Pubertal Boy With Growth Hormone Deficiency

Ping Zhou, MD; Bina Shah, MD; Kris Prasad, PhD; and Raphael David, MD


ABBREVIATIONS. AI, aromatase inhibitor; BMD, bone mineral density; GH, growth hormone; PTH, parathyroid hormone; IGF, insulin-like growth factor.

ESTROGEN plays a critical role for the pubertal growth spurt, skeletal maturation, and accrual and maintenance of bone mass in females as well as males. It is now evident that gene mutations of aromatase or estrogen receptor that result in impairment of estrogen production or action have similar phenotypes, including abnormally tall stature with eunuchoid proportions, a lack of pubertal growth spurt, unfused epiphyses, and osteopenia. Aromatase, encoded by the CYP19 gene located on chromosome 15q21.2 and expressed in bones, is the key enzyme for estrogen biosynthesis. It has been proposed that an aromatase inhibitor (AI) can be used to improve the final adult height in short pubertal boys. The hypothesis is that suppressing estrogen formation after the onset of puberty would delay the closure of the epiphyses, thus allowing for an extended period of growth without affecting the progression of androgenic development. Potential adverse effects of AIs, such as reduced bone mineral density (BMD), metabolic effects including a propensity for insulin resistance and dyslipidemia, and impairment of the hypothalamic-pituitary-gonadal axis, need to be considered. To date, a couple of studies, at least in the short term, indicate that the use of an AI is safe and promising.

As shown in Table 1, there was an initial increase in serum insulin-like growth factor 1 (IGF1) from 124 to 824 ng/mL, undoubtedly reflecting the effects of GH therapy, which was then maintained in the high to upper-normal range (reference: 182–839 ng/mL). Basal follicle-stimulating hormone ranged from 9 to 12 mIU/mL (reference: 1.2–11.0 mIU/mL), and luteinizing hormone ranged from 5 to 7 mIU/mL (reference: 0.2–7.0 mIU/mL), both of which are in the high-normal range. Serum testosterone still remained 2 SDs below his target height. Letrozole (2.5 mg/day) was added at 16 years 2 months, after which letrozole was discontinued. He tolerated the treatment well. Gynecomastia resolved within a few months after combination therapy. Pubertal maturation proceeded to Tanner V (testicular volume: 15–20 mL). After 17 months of treatment, he gained an additional 10 to 16 cm, and his bone age advanced only 2 years (Greulich-Pyle method). His height z score improved further, from −2.04 to −1.08 (Table 1), and his adult-height prediction as estimated by the Bailey-Pineau method improved from 166.4 to 175.3 cm, corresponding to his target height. His upper/lower segment ratio was maintained at 1.0. Weight gain was noticed during the course of treatment (Fig. 1). His BMI increased from 22 (76th percentile) to 24 (83rd percentile) after GH and to 27 (92nd percentile) after the addition of letrozole. Bone turnover markers were monitored. Four months after starting letrozole, the patient started to receive calcium supplementation (1200 mg/day) and vitamin D3 (400 IU/day) because of mildly elevated 1,25-(OH)2 vitamin D3 level of 78 pg/mL (reference: 27–71 pg/mL). Alkaline phosphatase was stable in the reference range, and PTH normalized after calcium and vitamin D supplementation. Bone markers including osteocalcin and N-telopeptide were decreased during therapy with letrozole and GH (see Table 1). Aerial bone density was determined by using a Hologic Dexa scanner (Bedford, MA), and the results were expressed as age-, gender-, and ethnicity-adjusted z scores. Although there was no pretreatment BMD study, a series of studies obtained at 4, 14, and 17 months during therapy actually showed some improvement of z score from −2.50 to −1.90. As shown in Table 1, there was an initial increase in serum insulin-like growth factor 1 (IGF1) from 124 to 824 ng/mL, undoubtedly reflecting the effects of GH therapy, which was then maintained in the high to upper-normal range (reference: 182–839 ng/mL). Basal follicle-stimulating hormone ranged from 9 to 12 mIU/mL (reference: 1.2–11.0 mIU/mL), and luteinizing hormone ranged from 5 to 7 mIU/mL (reference: 0.2–7.0 mIU/mL), both of which are in the high-normal range. Serum testosterone increased from 43 to 460 ng/dL after letrozole and then stabilized between 251 and 450 ng/dL (Tanner V; reference: 300–900 ng/dL). Serum...
Fig 1. Growth chart.
TABLE 1. Patient Data

<table>
<thead>
<tr>
<th>Time</th>
<th>Age</th>
<th>Height, cm</th>
<th>Score of height</th>
<th>BMI</th>
<th>Tanner stage</th>
<th>Bone age</th>
<th>Predicted adult height, cm</th>
<th>IGF1, ng/mL</th>
<th>FSH, mIU/mL</th>
<th>LH, mIU/mL</th>
<th>Testosterone, ng/dL</th>
<th>Estradiol, pg/mL</th>
<th>Intact PTH, pg/mL</th>
<th>Alkaline phosphatase, U/L</th>
<th>Osteocalcin, ng/mL</th>
<th>-Telopeptide, nM BCE/mM creatinine</th>
<th>N-BMD, z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 mo</td>
<td>15 y</td>
<td>144.5</td>
<td>2.94</td>
<td>22.0</td>
<td>2</td>
<td>13 y 6 mo</td>
<td>158.0</td>
<td>124.0</td>
<td>2.0</td>
<td>17.0</td>
<td>43.0</td>
<td>5.4</td>
<td>69.9</td>
<td>238.0</td>
<td>134.3</td>
<td>682.0</td>
<td>2.50</td>
</tr>
<tr>
<td>12 mo</td>
<td>15 y</td>
<td>146.0</td>
<td>2.92</td>
<td>22.0</td>
<td>2</td>
<td>14 y</td>
<td>162.2</td>
<td>607.0</td>
<td>10.0</td>
<td>17.0</td>
<td>460.0</td>
<td>6.0</td>
<td>50.3</td>
<td>287.0</td>
<td>115.0</td>
<td>398.0</td>
<td>7.00</td>
</tr>
<tr>
<td>8 mo</td>
<td>15 y</td>
<td>158.0</td>
<td>2.04</td>
<td>24.0</td>
<td>3</td>
<td>14 y 3 mo</td>
<td>159.5</td>
<td>824.0</td>
<td>12.0</td>
<td>4.0</td>
<td>390.0</td>
<td>8.0</td>
<td>270.0</td>
<td>340.0</td>
<td>23.0</td>
<td>170.0</td>
<td>1.90</td>
</tr>
<tr>
<td>4 mo</td>
<td>15 y</td>
<td>161.0</td>
<td>1.92</td>
<td>25.5</td>
<td>3</td>
<td>14 y 9 mo</td>
<td>161.0</td>
<td>740.0</td>
<td>9.0</td>
<td>5.0</td>
<td>270.0</td>
<td>9.0</td>
<td>300.0</td>
<td>340.0</td>
<td>321.0</td>
<td>280.0</td>
<td>1.70</td>
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<tr>
<td>0 mo</td>
<td>15 y</td>
<td>162.2</td>
<td>1.72</td>
<td>25.5</td>
<td>4</td>
<td>15 y 6 mo</td>
<td>162.2</td>
<td>664.0</td>
<td>11.0</td>
<td>4.0</td>
<td>300.0</td>
<td>9.0</td>
<td>22.0</td>
<td>375.0</td>
<td>31.0</td>
<td>-2.90</td>
<td>-1.90</td>
</tr>
</tbody>
</table>

DISCUSSION

The effect of estrogen on the dynamic processes of bone turnover is multifactorial. Its actions involve other hormones and factors such as GH, IGFs and their binding proteins, other growth and morphogenetic factors, thyroid hormone, vitamin D, retinoids, PTH and PTH-related peptide, cytokines, and their receptors. Although it is clear now that estrogen plays a major role in the pubertal growth spurt, skeletal maturation, and the accrual and maintenance of bone mass in both females and males, there is also evidence supporting a direct role for androgen on bone mass accrual. Manipulating hormone levels by AIs to decrease estrogen and increase androgen levels is an attractive option for extending the period of growth of short boys in puberty.

Our case documents a favorable outcome with GH and AI therapy in the enhancement of growth potential at least on a short-term basis. The adult-height prediction improved significantly while pubertal maturation proceeded unimpeded. Letrozole has been well tolerated by the patient. Potential adverse effects of AIs including decreased bone accretion and maturation and abnormalities in pubertal maturation have to be monitored carefully. Although BMD in our patient was at −2.5 (z score) after initiation of letrozole, it subsequently improved, which is likely because of the beneficial effect of GH and probably also the increase in endogenous testosterone. biochemical markers of puberty including serum testosterone, gonadotropins, and changes in the estradiol-to-testosterone ratio showed the expected effects of relative estrogen suppression, and the hormone levels eventually remained in the normal range for the pubertal stage.

After 17 months’ treatment of GH and letrozole, the lipid profile was normal. The only adverse finding was an indication of insulin resistance, with an elevated fasting insulin level. The cause of this insulin resistance (whether due to the patient’s excess weight or the treatment) is impossible to determine in this single case. Overall, the degree of the aromatase inhibition significantly improved height prediction without a negative impact on either the gonadotropin-testicular axis or bone health.

Recent studies by Dunkel and co-workers in Finland showed results generally consistent with our observations. The authors compared the effect of letrozole plus testosterone to testosterone alone in

estradiol was stable at 6 to 9 pg/mL (Tanner V; reference: 3–45 pg/mL) despite the pronounced rise in testosterone. Estradiol was assayed at the Mayo Medical Laboratories (Rochester, MN) by radioimmunoassay after extraction and chromatography; the testosterone assay was performed in our pediatric endocrine laboratory by a similar method. The estradiol-to-testosterone ratio decreased from 0.123 to 0.013 (a 9.4-fold decrease) after starting letrozole treatment, suggesting a relative suppression of estradiol. The estradiol-to-testosterone ratio was subsequently maintained in a range of 0.021 to 0.036 (a 3.8- to 5.9-fold decrease). Serial liver-function tests during and after letrozole treatment were normal.

Lipid profile and fasting plasma glucose were normal after 17 months of combination therapy, although the fasting insulin level was elevated at 41 mIU/mL. An oral glucose-tolerance test showed no impairment of glucose tolerance. The growth chart and hormonal and other data are presented in Fig 1 and Table 1.
treating boys with delayed puberty. After 18 months of treatment, their letrozole group increased the average predicted final adult height by 5.1 cm. In our own patient treated with comparable doses of letrozole in addition to GH, the predicted final height increased by 8.9 cm. It is encouraging to note that in the patients of Dunkel and co-workers, no detrimental effects on BMD were found.7

Gonadotropin-releasing hormone analog (GnRHa) therapy has been used for the treatment of short stature in pubertal boys and girls.14 Detrimental effects of GnRHa on body composition, muscle strength, and protein, lipid, and calcium metabolism, in addition to inhibiting virilization in males, have been the subject of several publications.15–17 These effects make the use of these analogs unsuitable in the long term if the sole purpose of treatment is to increase final height. The conclusion from a recent study by Yanovski et al stated that “treatment with an LHRH [luteinizing hormone-releasing hormone] agonist for 3.5 years increases adult height by 0.6 SD in adolescents with very short stature but substantially decreases bone mineral density. Such treatment cannot be routinely recommended to augment height. Thus, the use of a potent selective aromatase blocker offers the advantage of continued virilization and maintenance of pubertal body composition5,7 in boys while potentially delaying skeletal maturation. We therefore believe that the use of an AI with or without GH is a better option for enhancing the growth potential of short pubertal boys. Although our case and the Finnish studies showed a short-term benefit using an AI, long-term controlled studies are necessary to establish its safety and efficacy.

REFERENCES

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