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.1–4 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.2,4 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.5 To date, a couple of studies, at least in the short term, indicate that the use of an AI is safe and promising.6–8

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Fig 1. Growth chart.
TABLE 1. Patient Data

<table>
<thead>
<tr>
<th>Time</th>
<th>Age</th>
<th>GH (0.3 mg/kg per wk)</th>
<th>Letrozole (2.5 mg/d)</th>
<th>Height, cm</th>
<th>z score of height</th>
<th>BMI</th>
<th>Tanner stage</th>
<th>Bone age</th>
<th>Predicted adult height, cm</th>
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+ indicates off prescription; —, on prescription; BCE, bone collagen equivalents.

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 morphogenic 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...
treatment 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. 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. 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.”8(p908) 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.2

REFERENCES

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