CASE REPORT

Letrozole as a Booster Therapy in Growth Hormone Deficiency

KVS HARI KUMAR, MUTHUKRISHNAN JAYARAMAN, ABHYUDAY VERMA* AND KIRTIKUMAR D MODI

From the Departments of Endocrinology and Pediatric Endocrinology, Medwin Hospitals, Nampally, Hyderabad, AP, India.*

Correspondence to:
Dr Hari KVS Kumar,
Department of Endocrinology,
Medwin Hospitals,
Chirag Ali Lane, Nampally,
Hyderabad 500 001, AP, India.
hariendo@rediffmail.com
Manuscript received: April 1, 2008;
Initial review: April 23, 2008;
Accepted: July 4, 2008.

A 13 year old boy presented to us with short stature. Evaluation revealed growth hormone (GH) deficiency. He was treated with GH replacement for 10 months and to further boost up the growth potential, an aromatase inhibitor Letrozole was added to GH therapy. After one year of combination therapy, patient had significant improvement in predicted adult height without a negative impact on pubertal progression.

Key Words: *Aromatase inhibitors, Estrogen, Growth hormone, Letrozole.*

Estrogen is an essential regulator of bone maturation, growth plate fusion, and cessation of longitudinal growth(1). Therefore, an increase in adult height may be achieved in short children by blocking estrogen biosynthesis. Aromatase is the key enzyme for estrogen biosynthesis and aromatase inhibitors (AI) have been used primarily in women with breast carcinoma. The use of aromatase inhibitors may provide a means to delay skeletal maturation and increase final height in children with short stature(2).

Use of aromatase inhibitors to improve the final height has been extensively reported in idiopathic short stature or constitutional delay in puberty(3). However, the addition of aromatase inhibitor therapy to growth hormone (GH) in patients of GH deficiency is not widely studied(4). This combination may augment the growth potential and final height achieved in cases of GH deficiency. We report the pattern of growth in a child after addition of letrozole to GH therapy in a case of idiopathic growth harmone deficiency.

CASE REPORT

A male child was first seen for evaluation of short stature at the age of 13 years 8 months. He was a product of nonconsanguineous marriage with a birthweight of 3.2 kg, delivered after full term. He was treated for pulmonary tuberculosis at the age of 1 yr. His motor, mental milestones and scholastic performance in the school were normal. He was always amongst short children in the class but never sought any medical consultation. Parents denied noticing development of secondary sexual characteristics. There were no siblings and parents denied family history of delayed puberty. Anthropometry revealed: height – 140 cm (<5th centile), weight 48 kg (75th centile), upper/lower segment ratio 0.9, arm span – 142 cm, and puberty (Tanners grading) Stage 1 with prepubertal testes and bilateral lipomastia. His mid-parental height (MPH) was 173.5 cm. Examination revealed no midline defects, goiter or evidence of systemic disease. Estimated bone age was 11 yr by Greulich-Pyle method and his initial hematological and biochemical evaluation including thyroid/renal/

hepatic tests were normal. He was observed for 6 months and due to poor growth velocity (2 cm increase in 6 months) he was tested for GH deficiency after adequate priming. The peak GH levels following stimulation with clonidine was 0.26 ng/mL and GH deficiency was confirmed by low IGF1 - 50.3 ng/mL (131-718) and IGFBP3 – 809.7 ng/mL (1700-6940). His LH – 0.4 IU/L, FSH – 0.8 IU/L and testosterone – 120 ng/dL were prepubertal. He was initiated on GH therapy at the age of 14 yrs with a dose of 0.3 mg/kg/week. After 10 months of GH therapy, in view of height centile below his target height centile, the use of additional therapy to augment growth was planned and Letrozole was started at a dose of 2.5 mg daily along with GH therapy. The height improvement is shown in growth chart (***Fig.* 1**) and other clinical details are given in ***Table* I**. Due to significant improvement in stature without bone age advancement, we discontinued both GH and Letrozole after 1 year. The height velocity after therapy is about 13.5 cm per year over past 2 years with use of GH and Letrozole. The liver function tests and glycemic levels were normal throughout the period of observation. However, we did not evaluate any markers of bone turnover during the entire period of observation.

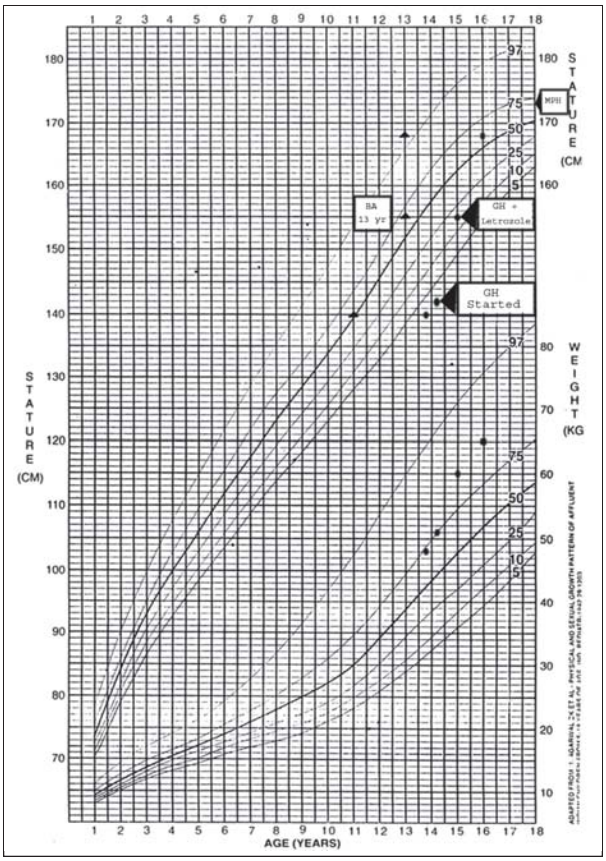

FIG.1 *Growth chart of the patient.*

DISCUSSION

Our case demonstrates the beneficial effect of letrozole along with GH therapy in augmenting the final adult height in a case of GH deficiency. The predicted adult height improved significantly while pubertal maturation proceeded unimpeded. Growth charts account for spontaneous pubertal progression and our patient demonstrated growth velocity of 13.5 cm per year, higher than seen with onset of spontaneous puberty in GH deficient individuals(5,6).

Growth response to therapy with GH is dependent on various factors(6). The available options to augment the growth response and final

TABLE I CLINICAL DETAILS OF PATIENT BEFORE AND AFTER THERAPY WITH GH AND LETROZOLE

Parameter	Pre treatment	On GH treatment alone	On GH + Letrozole therapy
Duration of Observation	6 months	10 months	12 months
Height gain (cm)	2	13	13
Height centile	< 5th centile	15th centile	65th centile
Growth velocity (cm/yr)	4	14	13
Bone age	11 yrs	11 to 13 yrs	Static
Predicted adult height* (cm)	170	174	181
Pubertal status	Tanner stage 1	Tanner stage 3	Tanner stage 4

* *As per Bailey & Pinneau charts.*

adult height are simultaneous use of gonadotropin-releasing hormone analogs (GnRHa) or aromatase inhibitors. The GnRHa therapy is associated with significant detrimental effects on metabolism and bone mineral density(7). These effects make the use of these analogs unsuitable for long term use. Thus, the use of AI offers the advantage of continued virilization and maintenance of pubertal body composition in boys while potentially delaying skeletal maturation. Our patient had a height increment of 13 cm during 10 months of GH therapy and combination therapy of GH and letrozole resulted in height increment of 13 cm in 12 months. This suggests that letrozole improves the final height in GH deficiency and augments the response to GH therapy as demonstrated by earlier observations(4).

Letrozole was well tolerated by our patient. Potential adverse effects of aromatase inhibitors are decreased bone matrix accumulation and delayed pubertal progression. However, we did not estimate bone mineral density in the child because of letrozole use for one year only and lack of standardization of dual energy X-ray absorptiometry scan in pediatric age group(8).

Contributors: KVS, JM, AV worked up the patient clinically. KVS, JM reviewed the literature and drafted the manuscript initially. KVS, KDM co drafted and revised the manuscript. KDM will act as the guarantor and the final manuscript was approved by all authors.

Funding: None.

Competing interests: None stated.

REFERENCES

1. Grumbach M, Auchus RJ. Estrogen: consequences and implications of human mutations in synthesis and action. J Clin Endocrinol Metab 1999; 84: 4677-4694.
2. Cernich J, Jacobson JD, Moore WV, Popovic J. Use of aromatase inhibitors in children with short stature. Pediatr Endocrinol 2004; 2: 2-7.
3. Hero M, Wickman S, Dunkel L. Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty. Clin Endocrinol 2006; 64: 510-513.
4. Zhou P, Shah B, Prasad K, David R. Letrozole significantly improves growth potential in a pubertal boy with growth hormone deficiency. Pediatrics 2005; 115: e245-248.
5. Grumbach MM. Estrogen, bone, growth and sex: a sea change in conventional wisdom. J Pediatr Endocrinol Metab 2000; 13 [Suppl 6]: 1439-1455.
6. Wit JM, Kamp GA, Rikken B. Spontaneous growth and response to growth hormone treatment in children with growth hormone deficiency and idiopathic short stature. Pediatr Res 1996; 39: 295-302.
7. Yanovski JA, Rose SR, Municchi G, Pescovitz OH, Hill SC, Cassorla FG, *et al*. Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. N Engl J Med 2003; 348: 908-917.
8. Binkovitz LA , Henwood MJ. Pediatric DXA: technique and interpretation. Pediatr Radiol 2007; 37: 21-31.