Aromatase Inhibitors Combined with Growth Hormone: A Cost-effective Last Chance for Improving Boys’ Stature at the Near-End of Growth?

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Commentary

Two studies have recently shown a clear benefit of using non-steroidal aromatase inhibitors (AIs) in combination with growth hormone (rhGH) in pubertal boys of very short stature (between -2.5 and -3 SDS) who are approaching the end of their growth [1,2]. AIs have been used in human therapeutics since the 1990s, mostly in adults [3], to block aromatase by binding to the heme iron of aromatase, a cytochrome p450 enzyme that catalyzes the formation of C18 estrogens (estrone and estradiol) from C19 androgens (androstenedione and testosterone) [4]. In males, circulating estradiol is derived from direct testicular secretion (20%) and from peripheral conversion of adrenal or testicular androgens [5,6].

AIs were proven to be safe, convenient and effective for the treatment of hormone sensitive breast cancer in women [7,8]. Since the early 2000s, pediatricians have used third generation non-steroidal AIs - anastrozole and the more potent letrozole- in adolescents with pubertal delay who are given testosterone to accelerate their sexual maturation [9-11]. AIs have also been used in boys who have precocious puberty [12]. They have been observed [1,2,14,19,20], possibly through an increase of fat-free mass. Vertebral abnormalities, mistakenly thought by a group of early investigators to be a secondary effect of letrozole [23], are now known to be common in untreated short adolescents [2,24-26]. BMD of lumbar vertebrae, the femoral neck, and markers of bone formation, such as alkaline phosphatase and osteocalcin, have been assessed in several of the published reports [9,21,27].

The data are reassuring and indicate that as puberty progresses, bone density increases similarly in subjects receiving AIs and in controls, with one study even reporting that volumetric BMD of the lumbar spine increased during AI administration [21]. Thus the short-term use of AIs has a reassuring track record for safety in pediatrics. Indeed, more than 250 adolescents treated with AI for periods of 0.5-3 years have revealed no serious secondary effects. Given their efficacy and their good safety profile, the potential for AIs to slow epiphyseal maturation resulting in longer linear growth has led to their use as an off-label growth therapy by pediatric endocrinologists [28].

Between 2004 and 2009, our group used a combination of rhGH (0.076 mg/kg) and anastrozole in an observational study of 11 adolescents aged 15.2 ± 0.8 yrs who had almost reached their adult height [1]. Although these adolescents were sexually mature and had a bone age at wrist of 14.5 ± 0.8 yrs, their femoral inferior and tibial superior growth plates were not entirely fused (knee score 2.8 ± 0.4), which qualified them for a therapeutic attempt. Treatment was pursued as long as growth rate remained significant, i.e. a mean total duration of 19 ± 6 months (6-24 months). Instead of the expected 157.9 ± 3.8 cm, a final height of 168.4 ± 2.6 cm was obtained in adolescents treated with rhGH and AIs (164.2 ± 5.6 cm in the rhGH alone group). This observation suggests that treatment with rhGH and AIs could allow a gain of 8-10 cm in adult height, superior by the 3-4 cm obtained with GH alone.

Comparable results were recently reported in a randomized study by Mauras et al. in 26 adolescents aged 14 ± 0.2 cm with bone age 12.7 ± 1 years and testosterone levels averaging 2.2 ± 2 ng/ml [2]. The sexual maturation and bone age were less advanced in these adolescents than in the previous study by ~2 years. Following 24-36 months of combined AIs (letrozole or anastrazole) and rhGH (0.042 mg/kg) treatment, final height reached 166.9 ± 6.5 cm after, compared to 164.8 ± 8 cm in those treated with rhGH alone. No secondary effects were observed.
except for a previously observed slight [20] increase in fat-free mass, which many adolescents may find desirable.

rhGH given alone in late puberty has a limited benefit on adult height [2], while AIs given alone seem to have no significant effect on adult height [29].

Combined rhGH and AIs administration seems to have a very good risk/benefit ratio in boys with [19,27,30] or without [2] growth hormone deficiency. On one side, rhGH has now demonstrated its long-term safety in patients with isolated growth hormone deficiency, idiopathic short stature or prenatal growth failure [31,32]. On the other side, the tolerance and efficacy of AIs makes them an attractive adjunct to rhGH to be used for growth promotion at the end of male adolescence, while their use remains precluded in pre-pubertal boys. Since published results are still restricted to a limited number of adolescents, larger studies are needed to evaluate the combined use of GH and AIs. If efficacy and safety are confirmed on a large scale, short periods (12-24 months) of treatment with combined rhGH and AI could become a cost-effective mean to increase the height of male adolescents near the end of their puberty and growth, a time when adult height can be accurately predicted.

References


