Commentry

iMedPub Journals
http://www.imedpub.com/

Journal of Clinical and Molecular Endocrinology
ISSN 2572-5432

2017
Vol.2 No.1:2

DOI: 10.21767/2572-5432.100036

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

Pierre Bougnères*

Pediatric Endocrinology, Hôpital Bicêtre, Paris Saclay University, Paris, France

***Corresponding author: Bougnères**, Pediatric Endocrinology, Hôpital Bicêtre, Paris Saclay University, Paris, France, Tel: 90 5334934643; Fax: 90 424 2379138; E-mail: pierre.bougneres@inserm.fr

Rec date: Mar 13, 2017; **Acc Date:** Mar 28, 2017; **Pub date:** Apr 02, 2017

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 several situations. One of the earliest pediatric use of letrozole has been to slow down the closure of epiphyseal plates in male 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 tested in pubertal gynecomastia [13,14], but due to lack of clear efficacy are not approved in this indication. AIs have also been used anecdotically by pediatricians in a few rare diseases, such as congenital adrenal hyperplasia [15,16], Peutz-Jeghers [17] or McCune-Albright syndromes [15-18].

Aromatase inhibitors were well tolerated and there were no withdrawals from any of the trials because of adverse effects. Only mild and transient elevations of testosterone and decrease of HDL-cholesterol within the physiological range have been observed [1,2,14,19,20]. After 2 years of 2.5 mg letrozole in boys aged 14.2 ± 1 year, mean testosterone level was 30 nmol/L, a physiological level which was four-fold higher than in placebo-treated boys [21]. Treatment with an aromatase inhibitor tended to cause a reduction in HDL-cholesterol at end of treatment of 0.26 and 0.47 mmol/L in two trials [11,21].

An increase of hemoglobin level occurred in patients in whom testosterone was given in addition of AIs, but does not occur if AIs are used without added testosterone, which stimulates erythropoiësis [22]. AIs have positive effects on insulin sensitivity [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 ± 3.8cm, 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

1. Rothenbuhler A, Linglart A, Bougneres P (2015). A randomized pilot trial of growth hormone with anastrozole versus growth hormone alone, starting at the very end of puberty in adolescents with idiopathic short stature. Int J Pediatr Endocrinol 4.
2. Mauras N, Ross JL, Gagliardi P, Yu YM, Hossain J, et al. (2016) Randomized Trial of Aromatase Inhibitors, Growth Hormone, or Combination in Pubertal Boys with Idiopathic, Short Stature. J Clin Endocrinol Metab. 101: 4984-4893.
3. de Ronde W, de Jong FH (2011) Aromatase inhibitors in men: effects and therapeutic options. Reprod Biol Endocrinol 9: 93.
4. Plourde PV, Dyroff M, Dowsett M, Demers L, Yates R, et al. (1995) ARIMIDEX: A new oral, once-a-day aromatase inhibitor. J Steroid Biochem Mol Biol 53: 175-179.
5. MacDonald PC, Madden JD, Brenner PF, Wilson JD, Siiteri PK (1979) Origin of estrogen in normal men and in women with testicular feminization. J Clin Endocrinol Metab 49: 905-916.
6. de Ronde W, Hofman A, Pols HA, de Jong FH (2005) A direct approach to the estimation of the origin of oestrogens and androgens in elderly men by comparison with hormone levels in postmenopausal women. Eur J Endocrinol 152: 261-268.
7. Perez EA, Josse RG, Pritchard KI, Ingle JN, Martino S, et al. (2006). Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: A companion study to NCIC CTG MA.17. J Clin Oncol. 24: 3629-3635.
8. Lonning PE, Geisler J, Krag LE, Erikstein B, Bremnes Y, et al. (2005) Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. J Clin Oncol. 23: 5126-5137.
9. Wickman S, Sipila I, Ankarberg-Lindgren C, Norjavaara E, Dunkel L (2001). A specific aromatase inhibitor and potential increase in adult height in boys with delayed puberty: a randomised controlled trial. Lancet 357: 1743-8.
10. Hero M, Wickman S, Dunkel L (2006). Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty. Clin Endocrinol (Oxf) 64: 510-213.
11. Salehpour S, Alipour P, Razzaghy-Azar M, Ardeshirpour L, Shamshiri A, et al. (2010). A double-blind, placebo-controlled comparison of letrozole to oxandrolone effects upon growth and puberty of children with constitutional delay of puberty and idiopathic short stature. Horm Res Paediatr. 74: 428-435.
12. Eugster EA (2004) Aromatase inhibitors in precocious puberty: rationale and experience to date. Treat Endocrinol 3: 141-151.
13. Mauras N Bishop K, Merinbaum D, Emeribe U, Agbo F, et al. (2009) Pharmacokinetics and pharmacodynamics of anastrozole in pubertal boys with recent-onset gynecomastia. J Clin Endocrinol Metab 94: 2975-2978.
14. Plourde PV, Reiter EO, Jou HC, Desrochers PE, Rubin SD, et al. (2004). Safety and efficacy of anastrozole for the treatment of pubertal gynecomastia: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 89: 4428-4433.
15. Cutler GB Jr, Laue L (1990) Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. N Engl J Med 323: 1806-1813.
16. Hawton K, Walton-Betancourth S, Rumsby G, Raine J, Dattani M (2017). Growth Hormone With Aromatase Inhibitor May Improve Height in CYP11B1 Congenital Adrenal Hyperplasia. Pediatrics 139.
17. Lefevre H, Bouvattier C, Lahlou N, Adamsbaum C, Bougneres P, et al. (2006). Prepubertal gynecomastia in Peutz-Jeghers syndrome: incomplete penetrance in a familial case and management with an aromatase inhibitor. Eur J Endocrinol 154: 221-227.
18. Tessaris D, Matarazzo P, Mussa A, Tuli G, Verna F, et al. (2012). Combined treatment with bicalutamide and anastrozole in a young boy with peripheral precocious puberty due to McCune-Albright Syndrome. Endocr J 59: 111-117.
19. Mauras N, Gonzalez de Pijem L, Hsiang HY, Desrosiers P, et al. (2008). Anastrozole increases predicted adult height of short adolescent males treated with growth hormone: a randomized, placebo-controlled, multicenter trial for one to three years. J Clin Endocrinol Metab. 93: 823-831.
20. Hero M, Ankarberg-Lindgren C, Taskinen MR, Dunkel L (2006). Blockade of oestrogen biosynthesis in peripubertal boys: Effects on lipid metabolism, insulin sensitivity, and body composition. Eur J Endocrinol 155: 453-460.
21. Hero M, Norjavaara E, Dunkel L (2005). Inhibition of estrogen biosynthesis with a potent aromatase inhibitor increases predicted adult height in boys with idiopathic short stature: a randomized controlled trial. J Clin Endocrinol Metab. 90: 6396-402.
22. Hero M, Wickman S, Hanhijärvi R, Siimes MA, Dunkel L (2005) Pubertal upregulation of erythropoiesis in boys is determined primarily by androgen. J Pediatr 146: 245-252.
23. Hero M, Toiviainen-Salo S, Wickman S, Makitie O, Dunkel L (2010). Vertebral morphology in aromatase inhibitor-treated males with idiopathic short stature or constitutional delay of puberty. J Bone Miner Res 25: 1536-1543.
24. Hero M, Makitie O, Kroger H, Nousiainen E, Toiviainen-Salo S, et al. (2009). Impact of aromatase inhibitor therapy on bone turnover, cortical bone growth and vertebral morphology in pre- and peripubertal boys with idiopathic short stature. Horm Res 71:290-297.

25. Ramadorai U, Hire J, DeVine JG, Brodt ED, Dettori JR (2014). Incidental findings on magnetic resonance imaging of the spine in the asymptomatic pediatric population: a systematic review. Evid Based Spine Care J. 5: 95-100.

26. Jaremko JL, Siminoski K, Firth GB, Matzinger MA, Shenouda N, et al. (2015). Common normal variants of pediatric vertebral development that mimic fractures: a pictorial review from a national longitudinal bone health study. Pediatr Radiol 45: 593-605.

27. Mauras N, Welch S, Rini A, Klein KO (2004). An open label 12-month pilot trial on the effects of the aromatase inhibitor anastrozole in growth hormone (GH)-treated GH deficient adolescent boys. J Pediatr Endocrinol Metab 17: 1597-606.

28. Dunkel L (2010) Off-label use of aromatase inhibitors to promote taller stature: is it safe. Horm Res Paediatr 74: 436-437.

29. Shams K, Cameo T, Fennoy I, Hassoun AA, Lerner SE, et al. (2014). Outcome analysis of aromatase inhibitor therapy to increase adult height in males with predicted short adult stature and/or rapid pubertal progress: a retrospective chart review. J Pediatr Endocrinol Metab 27: 725-730.

30. Zhou P, Shah B, Prasad K, David R (2005). Letrozole significantly improves growth potential in a pubertal boy with growth hormone deficiency. Pediatrics. 115: e245-248.

31. Albertsson-Wikland K, Martensson A, Savendahl L, Niklasson A, Bang P, et al. (2016). Mortality Is Not Increased in Recombinant Human Growth Hormone-treated Patients When Adjusting for Birth Characteristics. J Clin Endocrinol Metab 101: 2149-2159.

32. Swerdlow AJ, Cooke R, Beckers D, Borgstrom B, Butler G, et al. (2017). Cancer risks in patients treated with growth hormone in childhood: the SAGhE European cohort study. J Clin Endocrinol Metab.