Aromatase Inhibitors in Paediatric Endocrinology

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The availability of the 3rd-generation aromatase inhibitors (AIs) (anastrozole 1 mg, letrozole 2.5 mg, exemestane 25 mg) and clinical observations in males with aromatase deficiency have stimulated the therapeutic (off-label) use of AIs in children in four groups of conditions: 1) hyperestrogenism; 2) hyperandrogenism; 3) pubertal gynecomastia and 4) short stature and/or delayed puberty. In a recent review, the experience with the use of AIs in pediatrics was extensively discussed (1).

The scarce literature suggests that AIs may be efficacious, in the 3 rare conditions associated with hyperestrogenism (aromatase excess syndrome, Peutz-Jeghers syndrome and McCune-Albright syndrome). The main condition associated with hyperandrogenism, testostoxicosis (familial male-limited precocious puberty), appears to respond well to the combination of anastrozole and bicalutamide (a potent antiandrogen) (2). The effect on pubertal gynecomastia is unsatisfactory (3), although a later open-label study suggested some effect (4).

Four randomized studies have been published on the effect of AIs in short adolescent boys. The combination of 1 year of letrozole with 6 months of testosterone (T) treatment in boys with delayed puberty led to a 5.1 cm increase in predicted adult height (PAH) after 18 months and near adult height was 6.9 cm taller than with T alone (5). However, for such boys who had already entered into puberty, were not very short and had a normal predicted adult height, most clinicians would rather offer reassurance and/or short course of androgens. Furthermore, the combination with T has proven unnecessary and led to very high serum T levels.

In a 2nd Finnish study, boys with idiopathic short stature (ISS) (mostly prepubertal) were treated for 2 years with letrozole. They showed an increase of PAH of 5.9 cm after 2 years, but 4 years later, this had decreased to 4 cm (non-significant). Vertebral deformities were found in 5/11 patients (6). A 3rd study assessing the additional effect of 3 years of anastrozole treatment in growth hormone-treated pubertal boys showed a PAH gain of 6.7 cm versus 1 cm in controls, but no adult height data are available yet (7). A 4th study assessed the effect of 2-year letrozole treatment in comparison to placebo or oxandrolone in 91 short boys. Letrozole increased PAH by 6.1 cm in comparison to 1.4 and 1.9 cm in both other arms (8), but there are several methodological issues. A recent retrospective study in 27 short adolescent males showed no effect on PAH (9).

In conclusion, for all indications in paediatrics, the use of AIs is experimental and the safety profile is still insufficiently known.

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