Use of aromatase inhibitors in children and adolescents: what's new?

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Purpose of review

Aromatase inhibitors have been reported to increase height prediction in boys with short stature, and in boys and girls with gonadotropin-independent precocious puberty. The following review discusses data published since 2008 regarding the safety and efficacy of aromatase inhibitors in pediatric patients.

Recent findings

Third-generation aromatase inhibitors in combination with antiandrogens appear effective in preventing bone age advancement and virilization in boys with familial male-limited precocious puberty (FMPP). Letrozole, but not anastrozole, decreased bleeding episodes and bone age advancement in girls with McCune–Albright syndrome (MAS), despite ovarian enlargement. Letrozole-treated boys with idiopathic short stature (ISS) had no loss of bone density but were noted to have more vertebral abnormalities than a placebo group. Two years of letrozole therapy did not increase predicted adult height in pre and peripubertal boys with ISS when re-assessed 4 years after the treatment period.

Summary

Aromatase inhibitors together with an antiandrogen appear to be a very promising treatment for FMPP. Further longer-term studies with letrozole are needed in MAS. The prevalence of vertebral deformities should be evaluated prospectively in patients treated with aromatase inhibitors. Adult height data are still lacking in pediatric patients treated with aromatase inhibitors. Two years of therapy in pre and peripubertal short boys does not appear to increase adult height. Hemogram, lipids, and bone density should be periodically assessed in treated patients. Further controlled studies are needed to demonstrate safety and efficacy of aromatase inhibitors in pediatric patients.

Keywords

anastrozole, aromatase inhibitors, letrozole, pediatrics, precocious puberty, short stature

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Introduction

Aromatase inhibitors serve as adjuvant therapy for estrogen-responsive breast cancer and prolong lives [1,2]. Use in children and adolescents is still limited and off-label. However, there is a slowly growing experience with their use in the treatment of gonadotropin-independent precocious puberty in boys and girls, short stature in boys, and pubertal gynecomastia [3–5,6,7–9,10,11]. This review summarizes the small experience in these pediatric conditions with emphasis on data published since 2008.

Background

Aromatase is a cytochrome p450 enzyme that catalyzes the conversion of androgens to estrogens. The aromatase gene is located at chromosome 15q21.2 and is present in a variety of tissues including ovary, testis, breast, adipose tissue, brain, placenta and bone [12]. Tissue-specific expression results from the interplay of nine promoters that are differentially expressed in these tissues [13]. A detailed history of aromatase starting from early studies of estrogen physiology in the 1930s to current ongoing clinical trials with aromatase inhibitors has recently been published by Santen *et al.* [14••].

Men with congenital aromatase deficiency are tall (they do not fuse their growth plates), osteoporotic, glucose-intolerant, overweight, and hyperlipidemic, and may have impaired fertility [15]. Affected girls virilize *in utero*, resulting in ambiguous genitalia, hypergonadotropic hypogonadism at puberty with no breast development, and primary amenorrhea [16].

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In pediatrics, the potential use of aromatase inhibitors to block estrogen-mediated skeletal maturation is an attractive intervention for pubertal children with predicted short adult stature. Recent experience in pediatric patients is with the nonsteroidal third-generation aromatase inhibitors letrozole (2.5 mg) and anastrozole (1 mg). Both can be given orally once daily and cost approximately $13 a pill in the US (Walgreens, personal communication).

Use of aromatase inhibitors in gonadotropin-independent precocious puberty

The largest published experience using aromatase inhibitors in the treatment of familial male-limited precocious puberty (FMPP) is from the National Institutes of Health: 10 boys were given a first-generation aromatase inhibitor, testolactone, and a weak antiandrogen, spironolactone, with gonadotropin-releasing hormone agonist (GNRHa) deslorelin added when central precocious puberty was evident [3]. After 6 years of therapy, predicted adult height increased by a mean of 12.9 cm. Subsequently, Kreher *et al.* [4] reported the use of anastrozole in combination with bicalutamide (a potent antiandrogen) for 16 and 44 months in two boys with FMPP and noted striking reductions in pubertal progression, growth velocity and bone age progression without adverse effects. A more recent study of two brothers with FMPP and metaphyseal chondrodysplasia treated with the combination of anastrozole and cyproterone acetate for 4 years demonstrated reduced growth velocity, slowed bone age advancement and was well tolerated [17]. We have treated a boy with FMPP for 4.5 years with letrozole, bicalutamide and GNRHa, resulting in dramatic slowing of bone age advancement, and substantially improving adult height prediction (Lenz A, Shulman D, Eugster EA, *et al.*, unpublished data) (Fig. 1). A phase II study of combination therapy with varying doses of bicalutamide and anastrozole for the treatment of FMPP is currently underway (BATT, Bicalutamide Anastrozole Treatment for Testotoxicosis study, AstraZeneca, ClincalTrials.gov #NCT00094328). Overall, combination therapy with a third-generation aromatase inhibitor, antiandrogen, and GNRHa, though costly, appears to be very promising with regard to halting signs of virilization and increasing adult height in FMPP.

Precocious puberty due to the McCune–Albright syndrome (MAS) in girls can be associated with recurrent ovarian cysts, vaginal bleeding, progression of secondary sexual development and bone age advancement. Treatment of 27 girls with MAS for 1 year with anastrozole was ineffective in halting vaginal bleeding and no changes in ovarian or uterine volume were reported [6]. In this study, estradiol and testosterone levels did not change from baseline, possibly suggesting incomplete or ineffective aromatase blockade. No adverse effects were otherwise noted. A trial of letrozole in nine girls with MAS and precocious puberty treated for up to 36 months reported a slowing of growth rate and bone age advancement, and fewer episodes of vaginal bleeding [5]. Increased ovarian volume and cyst enlargement were observed by 24–36 months and one girl experienced ovarian torsion. Although the therapeutic usefulness of aromatase inhibitors for this condition appears less encouraging than for FMPP, further study, particularly with letrozole, a more potent aromatase inhibitor than anastrozole [18,19], is needed.

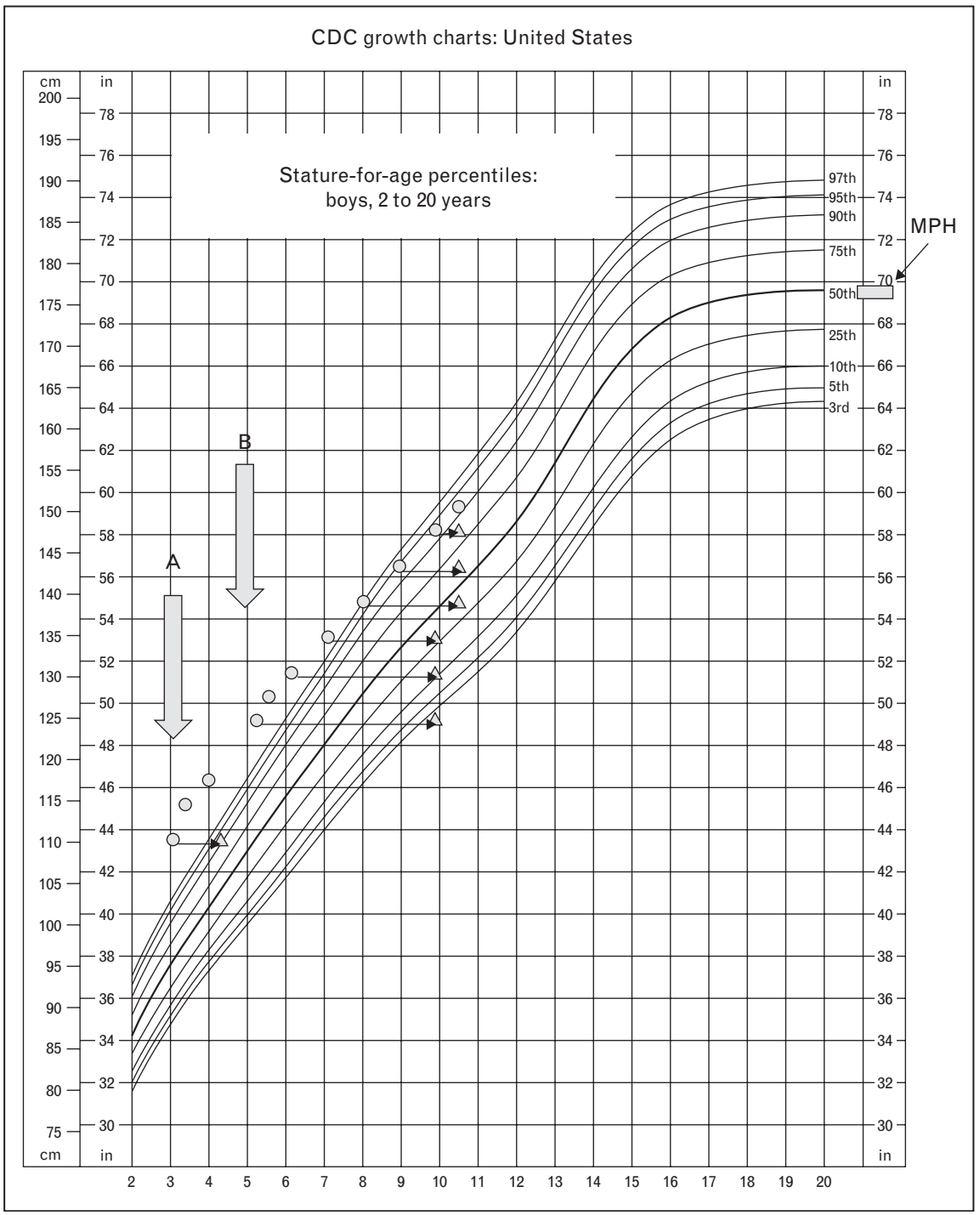
Pubertal gynecomastia

n 2004, Plourde *et al.* [11] reported a randomized, placebo-controlled study performed in adolescent boys with pubertal gynecomastia using anastrozole 1 mg daily vs. placebo. At baseline, breast tissue was present for at least 6 months and was stable or increasing. Six months later, ultrasonography of the breast tissue revealed reduction in 38 vs. 31% of boys in the anastrozole and placebo groups, respectively, which was not different. Breast pain decreased in both groups. Serum testosterone/estradiol ratio increased significantly in the treatment group (166 vs. 39%). The authors postulated that earlier treatment during the proliferative stage of breast development might have resulted in a greater effect of anastrozole. Mauras *et al.* [20•] recently studied the pharmacokinetics and pharmacodynamics of anastrozole. Forty-two adolescent boys with pubertal gynecomastia of less than 1 year's duration received 1 mg orally daily for 6 days [20•]. The drug was well tolerated; peak concentration was at 1 h and half-life was 46.8 h. At 6 months breast volume assessed ultrasonographically decreased by 57% compared with baseline measurement. Serum testosterone/estradiol ratio and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels increased, consistent with aromatase blockade. Further controlled studies are needed to assess the usefulness of aromatase inhibitors in reducing recent-onset pubertal gynecomastia.

Short stature

There have been three controlled studies examining the effects of aromatase inhibitors on height in boys with short stature [7,8,10]. The first included 23 Finnish boys (mean age 15.1 years) with constitutional delay in growth and puberty (CDGP) who were randomized to receive either testosterone enanthate 1 mg/kg intramuscular (i.m.) monthly for 6 months and letrozole 2.5 mg orally daily or placebo for 12 months [7]. At 18 months, the mean increase in predicted height in the letrozole-treated group vs. placebo was 5.1 ± 3.7 cm ($P < 0.004$). A follow-up evaluation [9] of 17 of the boys at near-adult height showed that the letrozole-treated group reached midparental

Figure 1



Growth chart of a boy with FMPP diagnosed at chronologic age (●) 3 years and started on testolactone and spironolactone (a). There was intermittent noncompliance associated with multiple daily dosing. At chronologic age 5.5 years bone age (▲) had advanced to 10 years. Patient was started on letrozole 2.5 mg and bicalutamide 50 mg orally daily (b). GNRHa therapy was initiated shortly afterward. There was no further advancement of bone age or signs of virilization over the subsequent 4 years. MPH, midparental height. Reproduced with permission from The National Center of Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health promotion.

height (175.8 vs. 177.1 cm; $P = 0.38$), whereas the placebo group did not (169.1 vs. 173.9 cm; $P = 0.007$). The treated group gained 1.4 SD over pretreatment height SDS compared with 0.8 SD in the placebo group ($P = 0.03$).

Hero *et al.* [8] subsequently enrolled 30 boys with idiopathic short stature (ISS) (mean age 11 years), the majority of whom were prepubertal (27 of 30). They were treated for 2 years with either letrozole 2.5 mg orally daily or placebo. After 2 years, 45% of the treated group and 58% of the placebo group were pubertal. Predicted height increased 5.9 cm in the letrozole group but not in the placebo group. No significant change in bone density was identified. A recent follow-up study of 23 of these boys performed 4.2 years after the end of treatment has shown that there is no longer a significant difference in median adult height prediction between groups (166.4 vs. 162.4 cm) [21••]. The authors suggest that therapy should be started only in pubertal patients and continued until a time (yet to be determined) that brings them nearer to adult height.

Mauras *et al.* enrolled 50 adolescent boys with biochemical growth hormone (GH) deficiency treated with GH approximately 0.3 mg/kg/week for at least 6 months and at least Tanner stage 2 genital development with bone age below 15 years [10]. Patients were randomized to receive either anastrozole 1 mg orally daily or placebo in addition to GH. At 24 months ($n = 41$) a net increase in predicted adult height of 4.5 ± 1.2 cm was observed in the anastrozole-treated group compared with the placebo group. At 36 months ($n = 28$) this difference increased to 6.7 ± 1.4 cm. No differences were observed in lipid levels, body composition or bone density. Adult height data will hopefully be forthcoming. Further data are needed to elucidate who will benefit from aromatase inhibitor therapy, when it should be initiated, and what is the optimal duration of treatment.

Adverse effects

In adult postmenopausal women being treated with aromatase inhibitors for breast cancer, musculoskeletal complaints are common [22]. Also, aromatase inhibitors appear to increase bone turnover and are associated with decreased bone density in this sex hormone-deficient population [23]. Musculoskeletal complaints have not been reported in children treated with aromatase inhibitors and bone density has not decreased on therapy. A recent study demonstrates that treatment with letrozole 2.5 mg orally daily for 2 years in peripubertal boys with ISS leads to increased cortical bone growth and decreased bone turnover compared with controls [24•]. The authors speculate that this may be due to a direct effect of elevated testosterone on bone. Vertebral body deformities were observed more commonly in post-treatment spinal radiographs but were also observed in control individuals.

Recently Hero *et al.* [21••] further investigated the impact of aromatase inhibitor therapy on vertebral morphology in the two cohorts of boys previously treated with letrozole [21••]. Spinal MRIs were performed and were analyzed for thoracic and lumbar vertebral anatomy and shape, endplate changes, disc height, water content and back muscle status. The shapes of all vertebral bodies were classified as normal, wedged, or compressed.

Cohort 1 included 23 of the 30 boys with ISS reported in reference [8] who were treated with letrozole or placebo for 2 years (end of treatment 4.2 years earlier). In the letrozole-treated group, five patients were observed to have eight vertebral body deformities in the thoracic spine: four mild (20–22%) anterior wedging deformities and four mild (21–23%) compression deformities ($P = 0.01$ vs. incidence in placebo group). Lesser (12–19%) anterior wedging deformities were found in six other participants, five of whom had received placebo. Endplate deformities were found in two patients treated with letrozole and five patients treated with placebo. No differences were observed in vertebral height indices, spinal muscle size, markers of bone turnover, or serum hormone levels.

Cohort 2 included 12 patients from the group of 23 Finnish boys with CDGP who had received testosterone in combination with either letrozole 2.5 mg or placebo daily for 12 months [7]. The study had concluded 7 years prior to the current spinal MRI analysis. MRI identified one patient in each group with mild vertebral deformities. Endplate deformities were seen in over half of the patients distributed between the groups. There were no differences in any parameter measured.

The authors observed increased vertebral abnormalities in the ISS cohort treated with letrozole but not in the CDGP group treated with letrozole. The ISS group was largely prepubertal at the start of treatment, was treated with letrozole for a longer time period, and it had been less time since the treatment (with perhaps a shorter time to 'heal'). The authors raise a concern that letrozole may disturb vertebral bone growth through estrogen deprivation or some other mechanism, and suggest prospective monitoring for vertebral anomalies in future studies. The numbers of patients in these analyses are small, and there are no data regarding the prevalence of vertebral abnormalities in normally growing children and adolescents with which to compare. Clearly, further prospective studies are needed to clarify the effects of aromatase inhibitors on all aspects of skeletal growth and bone mass accrual. Recently, calcitriol has been observed to modulate aromatase expression in a tissue-specific manner, upregulating aromatase expression in human osteosarcoma cells (used as surrogates for osteoblast cells) and downregulating activity in human breast cancer cells [25•].

Although no deterioration of bone density has been demonstrated in pediatric patients to date, it would seem prudent to assess vitamin D status and recommend at least standard doses of calcium and vitamin D supplementation in treated patients. Hero *et al.* [26] reported decreases in high-density lipoprotein cholesterol, a decrease in fat mass, but no changes in insulin sensitivity in boys treated with letrozole for 2 years. Mauras *et al.* [10] did not observe any change in fasting lipid or glucose concentrations in boys treated with GH with or without anastrozole. In long-term clinical trials of postmenopausal women, it appears that increases in low-density lipoprotein and total cholesterol levels are due to stopping tamoxifen rather than a direct lipid effect of aromatase inhibitors [27,28]. Interestingly, metformin, a drug commonly used in insulin-resistant pediatric patients with type 2 diabetes and polycystic ovarian syndrome, has recently been shown to reduce basal and insulin-stimulated aromatase expression and activity in human granulosa-luteal cells *in vitro*, shedding further light on its mechanism of action in ovulation induction [29•].

Aromatase inhibitors can cause supraphysiologic levels of testosterone (1240 ng/dl, 1450 ng/dl) in pubertal boys that may be associated with a significant elevation of circulating hemoglobin concentrations (16 g/dl, 17.5 g/dl) (Diaz-Thomas A, Shulman D, Root AW, unpublished data). High-dose testosterone therapy increased hemoglobin and hematocrit in two adult men with aromatase deficiency independent of estrogen [30]. In boys treated with testosterone and letrozole, increases in hemoglobin levels correlated with testosterone levels, independent of insulin-like growth factor-1 levels [31]. Testosterone levels may be higher in boys treated with letrozole (2.5 mg) than with anastrozole (1 mg) [8,10,11]. Although not reported, adolescent boys treated with aromatase inhibitors who develop erythrocytosis may be at increased risk for thrombotic events.

At least one man reported with congenital aromatase deficiency was documented to have poor sperm quality that could not be attributed to other factors [16]. Treatment of men in the short term with aromatase inhibitors does not seem to impair fertility. Pretreatment of Klinefelter patients with an aromatase inhibitor increased testosterone and improved sperm retrieval rates during microdissection [32]. Recently, treatment with letrozole resulted in normal spermatogenesis on testicular biopsy in a young man with primary infertility due to non-obstructive azoospermia [33], and restored fertility in another man with obesity-related hypogonadotropic hypogonadism [34]. In pubertal boys, Mauras *et al.* [35] evaluated sperm parameters in a group of GH-deficient boys treated with anastrozole several years later and found them to be no different from controls.

Estrogen deficiency is thought to affect the micro-architecture of the developing brain: female aromatase knockout mice (ARKO) have apoptosis and cell loss in the frontal cortex of the brain, whereas previous studies in male ARKO mice noted cell loss of dopaminergic neurons in the hypothalamus [36,37]. Estrogen may be important in limiting brain damage after an insult. In birds and mammals, locally produced aromatase in glial cells is induced by brain injury and has been associated with decreased secondary apoptotic damage [38••]. In adult female zebra finches, estrogen deprivation caused by centrally administered fadrozole (a nonsteroidal aromatase inhibitor) caused exacerbation of damage due to a targeted cerebellar lesion; estrogen replacement resulted in return of cognitive processing as measured by improvement in spatial tasks, but not motor recovery [39]. Studies in neonatal boars treated with the aromatase inhibitor etimodate revealed decreased aromatase activity in the testes but increased activity in the hypothalamus, suggesting differential tissue effects of aromatase inhibitors and differential regulation of aromatase expression in the brain compared with other tissues [40]. Aromatase inhibitors cross the blood–brain barrier. This was recently confirmed by positron emission tomography of the baboon brain after peripheral administration of [^{11}C-cyano] labeled letrozole [41]. Also, anastrozole 1 mg daily orally significantly reduced intracranial metastases assessed radiographically in an estrogen-responsive metastatic breast cancer [42].

No conclusive effects of aromatase inhibitors on cognition have been demonstrated in clinical trials. Cognitive testing at 6 and 24 months did not reveal significant changes from baseline in estrogen-deficient postmenopausal women treated with aromatase inhibitors [43]. Healthy older men (60–80 years) and younger men (25–35 years) were randomized to treatment with GNRHa and testosterone gel, GNRHa and testosterone gel and aromatase inhibitor, GNRHa alone, and placebo with measures of executive function, memory and spatial ability evaluated at baseline and after 6 weeks of treatment. No significant relationships between sex hormone levels and cognition were observed [44].

Conclusion

Since the introduction of aromatase inhibitors as adjuvant therapy for estrogen-sensitive breast cancer, their clinical applications have expanded coincident with the basic understanding of the tissue-specific functions and regulation of the aromatase enzyme. Insofar as letrozole is a more potent aromatase inhibitor, further studies of boys with FMPP or gynecomastia and girls with MAS should be performed comparing the effectiveness and safety profile of letrozole vs. anastrozole. Additional controlled studies in pubertal boys with ISS and CDGP with duration of

treatment longer than 2 years are needed before recommending use of aromatase inhibitor therapy to increase adult stature. Prospective studies of vertebral anatomy are needed to examine the relationship of aromatase inhibitor therapy to vertebral abnormalities recently reported. Investigation of the potential cognitive and neuroprotective effects of aromatase inhibitors on childrens' developing brains is also needed, as letrozole and anastrozole cross the blood–brain barrier. As long-term treatment data in children are still scarce, periodic assessment of hemogram, lipid panel, and bone density would seem prudent.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 554).

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