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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

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Abstract

Background—Aromatase inhibitors (AIs) have been used off-label to increase adult height in short adolescent males. Studies have shown that AIs increase the predicted adult height (PAH) while delaying bone age (BA) maturation. We sought to determine whether AI therapy increases PAH in boys with short stature or rapid pubertal progression, and to evaluate any untoward effects.

Methods—The charts of 27 boys with BA ≥ 13 and short stature [height ≥ 2 standard deviation (SD) below the mean or ≥ 2 SD below mid-parental target height (MPTH)] or rapid pubertal progress, treated with anastrozole were reviewed. Outcome measures included anthropomorphic, hormonal, and metabolic data.

Results—The AI therapy averaged 21 months (range 14–30 months) for all, with Rx group 1 receiving < 18 months therapy ($n = 7$) and Rx group 2 receiving 18–30 months therapy ($n = 20$). Post-therapy, in Rx group 1 and all subjects, there was no significant change in the PAH, height SDS, or BA/chronological age (CA). In Rx group 2, there was a small, nonsignificant increase in PAH, no change in height SDS, and a small decrease in BA/CA. Post-therapy PAH was different from MPTH in all and in both Rx groups 1 and 2, $p < 0.02$. Eight of them achieved near-final height, averaging 6.73 ± 1.40 cm less than MPTH and 1.91 ± 0.86 cm less than the pre-therapy PAH. Post-therapy, the initially decreased estradiol did not persist but mildly increased testosterone and decreased high-density lipoprotein were noted, as was an increase in hematocrit, and decrease in growth velocity.

Conclusions—We suggest that although bone age progression may be slightly delayed with longer duration of therapy, an overall short-term AI therapy does not lead to a final height that is greater than the predicted pre-therapy height.

Keywords

aromatase inhibitors; predicted adult height; short stature

Background

The function of aromatase inhibitors (AIs) is to block the aromatase enzyme (CYP 19) which promotes the conversion of androgens to estrogens. Due to the resulting decrease in production of estrogen, AIs have been used for many years in the treatment of estrogen-responsive breast cancer. Estrogen also plays an important role in regulating longitudinal growth during puberty by promoting the closure of epiphyses. If the production of estrogen is blocked, the fusion of the epiphyses may be delayed, potentially leading to a prolonged period of longitudinal growth and increased final adult height. This physiological effect has

been described in cases with inactivating mutations of the aromatase gene in which young men became very tall with unfused epiphyses even upon reaching adulthood (1).

The AIs are currently being used as an off-label treatment for short stature in adolescent males. According to some studies, the use of AIs can lead to a significant increase in predicted adult height (PAH) as well as an increased height standard deviation score (HtSDS) for bone age (BA) (2–4). However, data available regarding the actual attainment of final height following AI therapy are limited. A recent follow-up study showed that the initial difference in PAH had disappeared 4.2 years post-treatment (5).

Of additional concern is the limited safety profile of AI usage in the pediatric population. Untoward effects previously reported include possible alterations in vertebral bone growth and vertebral anomalies (5), decrease in high-density lipoprotein (4, 6, 7), and increase in hematocrit (8). The limited human data thus far available suggest no adverse effect of AI usage on insulin sensitivity (6, 7). However, a recent animal model study found that female Wistar rats treated with continuous 90-day administration of higher dose letrozole prior to puberty did show signs of insulin resistance including decreased insulin sensitivity and enlarged adipocytes (9). Potential effects on cognition and memory have not been extensively evaluated, though a recent trial suggested that AI therapy did not impact the cognitive performance (10).

In the current study, we performed a chart review of adolescent males who received AI therapy for short stature and/or rapid pubertal progress, to learn more about the efficacy of AIs as well as to document any untoward effects of this treatment.

Methods

Study design and subject selection

This retrospective chart review was approved by the institutional review board. All adolescent males followed in the outpatient clinics of the Department of Pediatric Endocrinology, Diabetes, and Metabolism at New York Presbyterian-Morgan Stanley Children's Hospital who were treated with AI therapy (anastrozole or letrozole) were considered candidates for the chart review, and were required to meet the following inclusion criteria:

- a. short stature [defined as the height at least 2 standard deviation (SD) below average, or at least 2 SD below mid-parental target height (MPTH)] and/or
- b. rapid pubertal progression with a BA $\geq$ 13 years.

Due to the retrospective nature of this chart review, we were unable to apply stricter inclusion criteria (such as treatment offered only to those boys with predicted height less than the MPTH). Subjects were excluded if they had a treatment duration of less than 12 months ($n = 8$), if they were receiving adjunctive therapy with growth hormone ($n = 15$), if they had clinically significant scoliosis (due to the difficulty in comparing heights after surgical treatment) ($n = 2$), or if they were receiving or had recently received hormonal medications such as testosterone or Lupron ($n = 2$). One additional subject with the diagnosis of gonadal dysgenesis was also excluded ($n = 1$). Some 55 charts were initially

reviewed and 27 among them were selected for analysis based on the aforementioned inclusion and exclusion criteria. All 27 subjects selected had received the same dose of anastrozole, i.e., 1 mg daily (three subjects who had received letrozole were excluded based on the above-mentioned criteria).

Methods

Anthropometric, hormonal, and metabolic data from years 2006 to 2012 were collected from charted visits up to 10 months prior to starting AI therapy, during AI therapy and up to 10 months following cessation of AI therapy, when available. All data collected were entered into a secure study database and subsequently de-identified by the co-authors. Outcome measures were changes in PAH, HtSDS, ratios of BA/chronological age (CA) post-therapy, near-final height, and effects on growth, pubertal development, hormonal and metabolic markers. Bone ages had been read by up to two endocrinologists and an average was taken if there was a discrepancy between the readings. The PAH was calculated from the BAs by the method of Bayley and Pinneau, using the Atlas of Greulich and Pyle (11).

PrePAH was based on the most recent BA prior to the start of therapy (preBA) while postPAH was based on the last available BA following the start of therapy (postBA). Subjects were divided into two groups based on the length of therapy (LOT): Rx group 1 for < 18 months (n = 7) and Rx group 2 for 18–30 months (n = 20). For purposes of analysis, LOT was taken at the time of the postBA, in which most subjects were at or immediately following the actual cessation of therapy. However, in eight subjects LOT was taken 2–5 months prior to cessation of therapy, and in one subject (Rx group 1), it was taken 9 months prior to the actual cessation of therapy.

Statistical analysis

Continuous variables were summarized with means and standard errors. Treatment group differences were assessed with independent t-tests (Rx group 1 or 2) while within-group pre-to post-changes and peak vs. pre-changes were assessed with two-tailed t-test against the null hypothesis of zero change. All subjects which contributed data were included in all analyses and no adjustment was made for multiple comparisons. A p-value < 0.05 was considered statistically significant.

Results

PAH, HtSDS, and bone age progression

The average preBA and postBA values were 13.6 ± 0.1 and 15.3 ± 0.2 years, respectively. The average CA values at the time of preBA and postBA were 13.7 ± 0.1 and 15.4 ± 0.1 years, respectively. The average MPTH was 172.52 ± 0.81 cm. The average LOT was 21 months, but ranged from 14 to 30 months.

The primary outcome measures were assessed for all subjects together, and for Rx group 1 and Rx group 2 separately (Table 1). Overall, there was no significant change in PAH, HtSDS, or the ratio of BA/CA for all subjects and for those in Rx group 1 post-therapy. In Rx group 2, there was a small increase in PAH that approached significance (2.03 ± 1.02

cm, $p = 0.11$), no change in HtSDS, and a small but significant decrease in the ratio of BA/CA post-therapy (0.03 ± 0.01 , $p = 0.02$). The ratio of postBA-preBA/postCA-preCA (DBA/DCA) was 0.86 ± 0.08 for all subjects, 1.14 ± 0.21 for Rx group 1, and 0.76 ± 0.08 for Rx group 2. The post-therapy PAH remained significantly different from MPTH in all subjects (169.42 ± 1.04 , $p = 0.005$), in Rx group 1 (166.55 ± 1.57 , $p = 0.008$), and in Rx group 2 (170.40 ± 1.22 , $p = 0.013$).

Near-final heights

We considered near-final height to have been reached in 8 out of the 27 subjects. Among these, 4 subjects had a BA ≥ 16 years and growth velocity ≥ 1 cm/year when compared to the height measured at a visit at least 3 months prior. Two subjects had growth velocities > 1 cm/year but were included as their BAs were 17 and 18 years. Two subjects had growth velocities ≥ 1 cm/year with BAs of 15 and 15.5 years obtained 2 and 1.5 years before, respectively. One of the latter two patients was initially classified as part of the < 18 months group (Rx group 1) because their post-therapy BA was obtained at 15 months post-treatment. However, we included him as one of the eight patients who had reached near-final height because at 26 months his growth velocity had declined to less than 1 cm/year.

Six out of eight subjects had discontinued AI therapy prior to the near-final height measurement, and the other two subjects completed the therapy within 1 month of the near-final height measurement.

The average LOT for this subgroup (the eight subjects above) was 20.6 months. The average near-final height was 163.96 ± 1.75 cm, which was 6.73 ± 1.40 cm (range: 1.52–13.54 cm) lower than the MPTH of the sample (169.88 ± 2.13 , $p = 0.002$). The near-final height was less than or equal to the prePAH in all eight subjects individually, and overall the average near-final height was not statistically different from the prePAH (163.96 ± 1.75 vs. 165.86 ± 1.42 cm, $p = 0.07$).

Growth and pubertal development

The average height pre- and post-therapy values were 152.40 ± 1.02 and 163.14 ± 0.86 cm, respectively ($p < 0.0001$). There was no change in the body mass index standard deviation score pre- and post-therapy (0.028 ± 0.177 vs. 0.020 ± 0.152 , $p = 0.58$). There was a significant decrease in the growth velocity post-therapy (7.9 ± 0.6 vs. 3.3 ± 0.3 cm/year, $p < 0.0001$). There was a statistically significant but clinically unremarkable difference between Tanner stage pre- and post-therapy (3.2 ± 0.1 vs. 4.2 ± 0.1 , $p < 0.0001$). Testicular volume increased significantly pre- vs. post-therapy (11.8 ± 0.6 vs. 17.7 ± 0.5 mL, $p < 0.0001$).

Hormonal and metabolic parameters

Testosterone—On therapy, testosterone increased to a peak of 802.0 ± 51.6 ng/dL, which was elevated from pre-therapy (349.4 ± 42.0 ng/dL, $p < 0.0001$). Post-therapy testosterone was 457.2 ± 54.5 ng/dL, which was statistically different from pre-therapy ($p = 0.03$).

Estradiol—On therapy, estradiol decreased to a nadir of 0.30 ± 0.06 ng/dL, which was different from the pre-therapy value of 1.14 ± 0.27 ng/dL ($p = 0.02$). Post-therapy estradiol was 1.20 ± 0.18 ng/dL, which was not different from pre-therapy ($p = 0.78$).

Insulin-like growth factor-1—Overall, there was no statistically significant change in insulin-like growth factor-1 (IGF-1) pre- vs. post-therapy (448.4 ± 22.7 vs. 429.8 ± 45.4 , $p = 0.40$).

Lipids—Low-density lipoprotein (LDL) was 85.0 ± 4.9 mg/dL pre-therapy, which was different from peak values while on therapy, 95.1 ± 4.5 ($p = 0.02$), but was not decreased overall post-therapy, 82.6 ± 5.2 mg/dL ($p = 0.62$). High-density lipoprotein (HDL) was 54.6 ± 2.7 mg/dL pre-therapy and decreased to a nadir of 43.0 ± 2.2 mg/dL on therapy ($p < 0.0001$). Post-therapy HDL was 50.5 ± 3.7 mg/dL and was lower than pre-therapy HDL ($p = 0.02$). There was neither a statistical decrease in cholesterol ($p = 0.71$), nor an increase in triglycerides (TG) post-compared to pre-therapy ($p = 0.32$); however these values were not routinely assessed in fasting state so are difficult to interpret.

Hematocrit—Pre-therapy, hematocrit was $41.3 \pm 0.6\%$ and was different from the peak value on therapy $45.9 \pm 0.6\%$ ($p < 0.0001$), and there was a small increase in post-therapy compared to pre-therapy hematocrit ($43.4 \pm 1.5\%$ vs $41.3 \pm 0.6\%$, $p < 0.03$). To be noted, post-therapy measurements were taken a minimum of 3 months after cessation of therapy.

Other changes—No clinically notable abnormalities were seen for hemoglobin A1C, glucose, and liver function tests. Two subjects stopped anastrozole due to coincident anxiety issues, which persisted 4–6 months after cessation of therapy. One subject stopped anastrozole due to heart palpitations and shortness of breath; however, a cardiology evaluation suggested exercise-induced bronchospasm as the likely diagnosis. One subject noted worsening in acne on anastrozole and considered stopping therapy, however, the acne subsequently improved while still on therapy. Apart from one subject that missed a week of anastrozole therapy due to insurance coverage issues, no other issues with compliance were noted upon chart review (Table 2).

Discussion

In this chart review, we have shown that AI therapy did not change the PAH or HtSDS in our subject sample, however, there may be a delay in BA progression that is more pronounced with longer duration of therapy. The fact that we only observed both a significant decrease in the delta BA/CA post-therapy along with a BA/CA of 0.77 in Rx group 2 lends support to this suggestion. Prior studies have also shown a more prominent change in BA with longer duration of therapy (4), as well as BA/CA value approaching 0.62 after 2 years of therapy (2). We did observe BA advancement in Rx group 1 (where BA/CA was > 1), however, this initial advancement of BA in the shorter duration of treatment likely reflects an inability to alter the ongoing prior effects of estrogen at the bone receptor level.

The near-final heights achieved by a smaller subject sample were substantially lower than their MPTHs, and for some, were even less than the pre-therapy prediction. We hesitate to speculate on an etiology for these findings as they are based on a limited number of subjects.

Hormonal alterations associated with treatment were as anticipated. The large increase in testosterone during therapy does not seem to be associated with any complications, and levels return to just slightly above baseline after the therapy is completed. The small decrease in HDL during therapy has been noted in other studies of AIs (4, 6, 7, 12). Furthermore, increased serum testosterone has been associated with lower HDL in adolescent males, perhaps via a mechanism involving apolipoproteins A-I and A-II (13). The small decrease in LDL post-therapy was not clinically significant. The alterations observed in cholesterol and TGs are difficult to interpret given that the samples were not routinely fasting, but prior studies of AIs have shown no change in these parameters (6, 7). Erythrocytosis has been previously reported with AI therapy and is likely to be considered as an androgen-mediated process (8, 14). The increase in hematocrit values reported here, however, was not clinically significant. The decrease in growth velocity, as expected, has also been noted in a previous study (5). To be noted, we observed no significant changes in IGF-1 with therapy. Previous studies have reported a range of inconsistent findings related to circulating IGF-1 levels; including increased IGF-1 levels in the placebo group compared to those on AIs post-therapy (2, 15), increased levels in both AI and placebo groups (4), and unchanged IGF-1 levels with AI therapy (6).

Finally, an inherent pitfall was that the study design was a retrospective chart review rather than a randomized placebo-controlled trial. The majority of our practitioners had a personal preference to prescribe a lower-potency AI, arimidex (3, 4) so our conclusions, as such, are limited and differ from other studies which mainly used letrozole (3, 4, 9). This study design also resulted in a heterogeneous patient population. Finally, as this was not a prospective protocol, the results should be interpreted with a modicum of caution.

Conclusions

In summary, we cannot from this pilot data suggest that AI therapy results in any changes in PAH in the attainment of MPTH, or that it improves final height when compared to the pre-therapy prediction. Given the lack of long-term safety data on AIs, one must continue to weigh the risks and benefits of such height augmentation therapy in the pediatric/adolescent population and pursue more prospective long-term outcome analyses.

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Table 1

Changes in PAH, HtSDS, and bone age progression with AI therapy.

	PAH, cm	HtSDS	BA/CA	BA/ CA	MPTH, cm
All subjects (n = 27)					
Pre	167.84 ± 0.94	-1.10 ± 0.11	0.997 ± 0.008	0.86 ± 0.08	172.52 ± 0.81, * p = 0.005
Post	169.42 ± 1.04	-1.05 ± 0.11	0.980 ± 0.014		
p-Value	1.57 ± 1.04	0.06 ± 0.08	-0.018 ± 0.010	0.08	
Rx group 1 (n = 7)					
Pre	166.22 ± 1.85	-0.84 ± 0.17	1.035 ± 0.018	1.14 ± 0.21	174.22 ± 1.17, * p = 0.008
Post	166.55 ± 1.57	-0.90 ± 0.20	1.043 ± 0.027		
p-Value	0.33 ± 2.24	-0.06 ± 0.22	0.008 ± 0.022	0.73	
Rx group 2 (n = 20)					
Pre	168.40 ± 1.22	-1.20 ± 0.14	0.984 ± 0.008	0.76 ± 0.08	171.91 ± 0.99, * p = 0.013
Post	170.41 ± 1.22	-1.10 ± 0.13	0.958 ± 0.014		
p-Value	2.01 ± 1.17	0.10 ± 0.09	-0.027 ± 0.010	0.02	

Changes in PAH, HtSDS, and BA/CA pre and post-therapy, separately for all subjects, Rx group 1 and Rx group 2. * indicates difference between post-variable and pre-variable. Also includes the BA/ CA (change in BA/change in CA) post-therapy for each subject group as well as the MPTH, which is compared to the postPAH

* p-Values indicated.

Table 2

Hormonal and metabolic parameters with AI therapy.

Parameter	Pre-therapy	On therapy peak or nadir (*)	Post-therapy	p-Value [pre vs. peak or pre vs. nadir(*)]	p-Value (pre vs. post)
Testosterone, ng/dL	349.4 ± 42.0	802.0 ± 51.6	457.2 ± 54.5	< 0.0001	0.03
Estradiol, ng/dL	1.14 ± 0.27	0.30 ± 0.06(*)	1.20 ± 0.18	0.02(*)	0.78
LDL, mg/dL	85.0 ± 4.9	95.1 ± 4.5	82.6 ± 5.2	0.02	0.62
HDL, mg/dL	54.6 ± 2.7	43.0 ± 2.2(*)	50.5 ± 3.7	< 0.0001(*)	0.02
Cholesterol, mg/dL	155.4 ± 5.2	162.5 ± 4.4	149.5 ± 5.0	0.12	0.71
TG, mg/dL	79.1 ± 9.0	131.2 ± 16.0	86.5 ± 12.8	0.03	0.32
Hematocrit, %	41.3 ± 0.6	45.9 ± 0.6	43.4 ± 1.5	< 0.0001	0.03
IGF-1, ng/mL	448.4 ± 22.7		429.8 ± 45.4		0.40

Hormonal and metabolic parameters prior to, during, and following cessation of AI therapy. LDL, low-density lipoprotein; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; TG, triglycerides.