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Near Final Height in Males treated with Aromatase Inhibitors

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ABSTRACT

Objective: Data on the impact of aromatase inhibitor (AI) therapy on final or near-final adult height (FNFH) in males with short stature is limited. This study investigated whether AI therapy improved FNFH in males with advanced or rapidly advancing bone age (ABA) and compromised predicted adult height.

Methods: Data were collected through retrospective chart review. Descriptive statistics were used to characterize the study cohort. Fisher's exact test and the Wilcoxon rank-sum test were used to compare outcomes.

Results: Of 72 patients reviewed, 59 (82%) received anastrozole, 11 (15%) received letrozole, and 2 (2.8%) switched from anastrozole to letrozole. Median treatment duration was 25 [interquartile range (IQR): 18-32] months. Most common diagnoses included growth hormone (GH) deficiency (31%), early puberty and premature adrenarche (18%), idiopathic short stature (15%), overweight/obesity (14%). GH was used in 66%. The overall median gain in height (FNFH minus initial predicted height) was 1.2 cm (IQR: -1.9-4.2). Letrozole-treated patients showed a greater median height gain (4.2 cm, IQR: 0.6-13) compared to the anastrozole group (0.8 cm, IQR: -2.6-3.5; $p=0.013$) and reached a FNFH closer to mid-parental height ($p=0.031$). Longer duration of treatment, therapy at earlier puberty stages, and GH therapy were all significantly associated with greater gain in height (p values=0.005, 0.012, and 0.022, respectively).

Conclusion: Our findings suggest that letrozole is associated with greater gain in height compared to anastrozole in males with ABA. Other factors associated with greater gains are treatment at earlier stages of puberty, longer duration of treatment and concurrent GH therapy.

Keywords: Near final height, aromatase inhibitor, anastrozole, letrozole, advanced bone age, compromised height prediction

What is already known on this topic?

Aromatase inhibitors (AIs) are prescribed off-label in boys with accelerated bone maturation and reduced predicted adult height. Current literature offers limited and conflicting evidence regarding their effect on near-final or final height.

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What this study adds?

Letrozole was associated with greater gain in height compared to anastrozole (mean 4.2 vs 0.8 cm) in males with advanced bone age. Other factors associated with greater gains are treatment at earlier stages of puberty, longer duration of treatment and concurrent GH therapy.

Introduction

Aromatase, a member of the P450 enzyme family, catalyzes the conversion of androgens into estrogens by removing a methyl group at the carbon 19 position of the androgen molecule. This process results in the formation of phenolic 18-carbon estrogens. Aromatase Inhibitors (AIs) act by binding to aromatase and inhibiting its action, thereby decreasing estrogen production. They are FDA-approved for the treatment of hormone receptor-positive breast cancer as well as male gynecomastia (1). In the United States, commonly used AIs include letrozole and anastrozole.

Estrogen is known to play a significant role in growth plate senescence and epiphyseal fusion in both males and females, ultimately leading to cessation of linear bone growth after puberty (2,3). Genetic disorders that cause estrogen deficiency or resistance can disrupt the normal growth plate closure and lead to continued growth into adulthood. Aromatase mutations can result in decreased estrogen production, leading to delayed or incomplete growth plate fusion (4). Similarly, mutations in the estrogen receptor can lead to impaired estrogen signaling, preventing growth plate closure, whereas early exposure to estrogen, such as in early/precocious puberty, can lead to early growth plate fusion and short stature (5). AIs have been used off label in the treatment of males with short stature as it is believed that they can postpone growth plate closure and extend the period of linear bone growth, thus improving adult height.

Previous studies have demonstrated the potential of AI therapy to enhance the predicted adult height (PAH) of males undergoing treatment for various conditions, including idiopathic short stature (ISS), growth hormone (GH) deficiency (GHD) and constitutional delay of growth and puberty (CDGP). Mauras et al. (6,7) showed that anastrozole, when used concurrently with GH in males with GHD, resulted in a significant increase of the PAH, with a 4.5 +/- 1.2 cm increase after 24 months and a 6.7 +/- 1.4 cm increase after 36 months of therapy. In a separate study, the same group also showed that 24 months of anastrozole therapy led to a 0.5 increase in height standard deviation score (SDS) in boys with ISS (6,7). Hero et al. (8,9) studied 31 boys diagnosed with ISS, treated with either letrozole or placebo and documented a 5.9 cm increase in the PAH of boys in the letrozole group. In a different study, they found that boys with CDGP treated with letrozole attained a higher mean near-final height, which did not significantly differ from their mid parental height (MPH) compared to boys on placebo (8,9). More recently,

Yackobovitch-Gavan et al. (10) reported that AI treated pubertal boys with short stature achieved greater adult heights when compared to both untreated controls and their baseline PAH.

Anastrozole and letrozole are both third-generation, highly potent, non-steroidal AIs. However, studies in postmenopausal women with breast cancer have shown that letrozole is more effective in suppressing total body aromatization and lowering estrogen levels compared to anastrozole (11). Results from pediatric studies comparing their impact on growth potential have been mixed. Pedrosa et al. (12) compared children treated with letrozole or anastrozole with or without GH and found that the letrozole + GH group had an increase in PAH that was significantly higher than the other groups. In contrast, Zegarra et al. (13) reported a minimal 1.3 cm increase in the PAH of patients treated, with no significant differences between the two drug groups. When comparing hormonal changes the letrozole group had a greater increase in the testosterone levels and a greater decrease in the estradiol levels (13). Studies investigating AI safety and particularly their impact on bone health have also produced equivocal data. Hero et al. (14) found no significant differences in the bone mineral density (BMD) between boys with ISS treated with letrozole or placebo 12 months after completing treatment. However, vertebral deformities were reported in 6 out of 13 boys in the letrozole group and 4 out of 11 boys in the placebo group. On the other hand, Zegarra et al. (13) reported a significant decrease in whole body and lumbar spine BMD Z-scores among boys treated with AIs, with a greater reduction in the letrozole group.

Collectively, these studies highlight the potential of AIs to delay the bone age progression and enhance PAH. However, further studies are warranted to assess their efficacy in improving final adult height among males with other diagnoses associated with compromised height potential and accelerated bone age. In addition, data comparing the efficacy and safety of the two different available agents, anastrozole and letrozole, remain limited. Therefore, the aim of the present study was to analyze data of male patients treated with AIs who have attained final or near-final adult heights (FNFH).

Methods

Study Design

This study was a retrospective chart review of male patients treated with AIs (anastrozole, letrozole) in the pediatric endocrinology clinic at Weill Cornell Medicine (WCM) between

2007 and 2022. Patients were selected based on predefined inclusion and exclusion criteria. The study was conducted in accordance with the guidelines and protocols approved by the Institutional Review Board (IRB) and all research procedures adhered to the ethical standards and regulations set forth by the IRB. The study protocol was reviewed and approved by the Weill Cornell Medicine Research Integrity IRB and determined to qualify for exemption per the Code of Federal Regulations on the Protection of Human Subjects (WRG submission number: 23-08026421-02, FWA number: FWA00000093, date: 29.12.2023). Data was collected and managed in REDCap.

Inclusion and Exclusion Criteria

Male patients treated with AIs for a height prediction below their MPH or more than 2 SD below the population mean and advanced or rapidly advancing bone age (ABA) were included in the study. Exclusion criteria included: duration of AI treatment of less than one year; initiation of treatment before age nine years; nonadherence to therapy (as documented on follow up notes reviewed during chart review); concurrent treatment with a luteinizing hormone-releasing hormone analogue; or lack of data on final or near final height (NFH). NFH was defined as a bone age ≥ 16 years or growth velocity < 2 cm/yr.

Data and Outcomes

Data collected from medical records included patient demographics (race/ethnicity, insurance status), anthropometric measurements including height (cm) and height SDS at treatment initiation and during therapy, weight and BMI percentiles at the same time points, PAH at baseline and during treatment, bone age results, laboratory findings, duration of AI therapy, primary diagnosis, concurrent treatments and testicular volume at the start of treatment. Bone ages were interpreted by the senior pediatric endocrinologists of the WCM clinic. PAH were calculated according to the Bailey and Pinneau method, applying the reference tables for “average” boys to avoid the significant overestimation of adult height that has been shown to occur in children with advanced bone age when the accelerated reference tables are used (15).

Primary outcomes included: gain in height (defined as the difference between FNFH and baseline PAH); gain in predicted height (defined as the difference between the final PAH and baseline PAH); and the final height discrepancy (defined as the difference between FNFH and MPH). Secondary outcomes included: change in bone age over time; occurrence of medication-related adverse effects; and associations between treatment efficacy and these variables - type of AI used, underlying diagnosis, age, pubertal stage at treatment initiation, duration of therapy and presence or absence of concurrent

growth hormone therapy. Patients who transitioned from one AI type to the other were excluded from the analyses comparing the efficacy between the two AI types to avoid confounding.

Statistical Analysis

Descriptive statistics were used to characterize the study cohort. Categorical variables are represented as frequency (percent), and continuous variables are represented as median (interquartile range; 25th-75th percentile). The Fisher's exact test and Wilcoxon rank-sum test were used to examine the association between clinical variables of interest and outcome measures. The difference in bone age across time points and between treatment groups was assessed using the Skillings-Mack test, which accounts for the missingness in follow-up. Multivariable linear regression was performed for gain in height with treatment (letrozole vs anastrozole) and receipt of GH treatment (yes vs. no) as predictors. Adjusted betas and 95% confidence intervals (CIs) were estimated from the multivariable model. All p values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in R Version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

A total of 72 patients treated with AIs were included. Of these, 59 patients (82%) received anastrozole only, 11 (15%) received letrozole only, and 2 (2.8%) transitioned from anastrozole to letrozole during the course of treatment due to persistently rapid advancement of bone age despite anastrozole therapy following chart review. Anastrozole was prescribed at 1 mg daily and letrozole at 2.5 mg daily with no dose adjustments during the treatment course. The majority of patients identified as White (62%) and were privately insured (94%). The median duration of AI therapy was 25 (18-32) months.

The overall median height and BMI at initiation of treatment were 154 (148-158) cm or -0.92 (-1.50 to 0.14) SD and 63rd (38th-89th) percentile respectively, while the overall median FNFH and final BMI were 169 (165-174) cm or -0.71 (-1.31 to -0.14) and 74th (50th-86th) percentile respectively. There was no significant difference in baseline median height in the anastrozole and letrozole groups (155 cm, IQR: 148-159 versus 151 cm, IQR: 143-158, $p=0.33$ or -0.92 SD, IQR: -1.53 to 0.12 versus -0.77 SD, IQR: -1.16 to 0.31, $p=0.91$). However, the FNFH in cm was significantly higher in the letrozole group (168 cm, IQR: 165-172 versus 173 cm, IQR: 168-179, $p=0.042$). FNFH SD did not differ between the two groups (-0.82 SD, IQR: -1.35 to -0.21 versus -0.15 SD, IQR: -0.56-0.26, $p=0.1$). No significant differences were observed between the two groups in median BMI at treatment initiation or at final follow-up (treatment initiation BMI 61st percentile,

IQR: 38th-89th versus 73rd percentile IQR: 35th-96th, p=0.51 and final BMI 70th percentile, IQR: 50th-87th versus 77th percentile, IQR: 43rd-82nd, p=0.98).

The median chronological age at treatment initiation was 13.3 (12.3-14.2), and 15.5 (14.8-16.2) years at the end of treatment. The median bone age at treatment initiation was 14 (13-14.3) years, with a median final bone age of 15.5 (15-16) years. Median testicular volume at treatment initiation was 12 (8-15) mL.

Diagnoses included GHD) (31%), early or rapid progression of puberty and premature adrenarche (18%), ISS (15%), overweight/obesity (14%), short stature not meeting criteria for ISS (13%), small for gestational age (9.9%), ABA only (9.9%), congenital adrenal hyperplasia (CAH) (4.2%) and other conditions (14%). All patients with GHD had isolated GHD, confirmed by two-agent GH stimulation testing. Among the 10 patients with overweight/obesity, 6 had concurrent GHD, and 4 were treated for ABA with compromised adult height prediction only.

Concurrent GH therapy was used for 47 patients (66%) with an overall median treatment duration of 42 (27-65) months. The median starting GH dose was 0.29 (0.25-0.30) mg/kg/week and the median maximum dose was 0.34 (0.3-0.37) mg/kg/week. There was no significant difference between the two groups in GH treatment duration or starting or maximum dose (41 vs 43 months, p=0.70; 0.29 vs 0.29 mg/kg/wk, p=0.60; and 0.34 vs 0.33 mg/kg/wk, p=0.86, respectively).

Outcomes

The overall median gain in height was 1.2 (-1.9 to 4.2) cm, while the median gain in predicted height was 3 (0-6) cm. The overall median final height discrepancy was -4.8 (-7.8 to -0.1) cm. Letrozole-treated patients showed a greater median gain in height of 4.2 (0.6 to 13) cm compared to those treated with anastrozole who gained 0.8 (-2.6 to 3.5) cm; p=0.013), as well as a smaller final height discrepancy [0.5 (-3.1 to 1.4) cm versus -5.8 (-8.0 to -2.3; p=0.036) cm] (Table 1). When adjusting for GH therapy, letrozole patients had on average a 7.5 cm greater gain in height (95% CI: 1.8 to 13) compared to anastrozole patients (p=0.011).

Longer treatment duration (p=0.005), earlier pubertal stage at treatment initiation (p=0.012) and concurrent GH therapy (p=0.022) were all associated with greater gain in height. Longer treatment duration and concurrent GH therapy were also associated with smaller final height discrepancies (p=0.002 and p<0.001, respectively) (Table 2A-C). Patients who received concurrent GH therapy had on average a 5.9 cm greater gain in height (95% CI: 1.4, 10, p=0.012), adjusting for treatment type. No significant differences in gain in height, gain in PAH and final height discrepancy were observed across the different diagnosis groups. AI therapy showed slower bone age advancement across treatment groups (p=0.025), but no difference was found between treatment groups over time (Figure 1A, 1B).

Adverse Effects/Laboratory Changes

Patient reported adverse effects included acne in 30 individuals, mental health concerns reported by six, including aggressive behavior, anger issues, and anxiety and depression, and hair loss in two. Laboratory abnormalities were also noted and included elevated liver function tests with six patients experiencing AST elevation, three patients ALT elevation and nine patients total bilirubin elevation. Elevations in AST and ALT resolved on repeat testing or after discontinuation of therapy in 5 out of 7 patients. One patient discontinued anastrozole due to elevated liver function tests but he was already nearing the end of his treatment course at the time of discontinuation. Among those with bilirubin elevations, two had elevated bilirubin at baseline that continued throughout treatment, while four showed normal levels on follow-up testing after completion of therapy. Testosterone levels increased compared to baseline during treatment follow-up (Table 3). No significant difference was noted on adverse effects and laboratory changes between the anastrozole and letrozole groups.

Discussion

Data on the off-label use of AIs to improve adult height in males with compromised PAH and ABA remain limited and inconsistent. Some studies suggest that boys with ISS with a PAH <-2.5 SD treated with a combination of GH and anastrozole

Table 1. Anastrozole vs. letrozole

	n	Overall	Anastrozole (n=59)	Letrozole (n=11)	p value
Gain in height (cm)	69	1.2 (-1.9-4.2)	0.8 (-2.6-3.5)	4.2 (0.6-13)	0.013
Gain in predicted height (cm)	68	3 (0-6)	2 (0-5)	7 (3-19)	0.011
FNFH-MPH (cm)	64	-4.8 (-7.8 to -0.1)	-5.8 (-8 to -2.3)	0.5 (-3.1-1.4)	0.036
Predicted height/MPH	64	0.97 (0.94-0.98)	0.97 (0.95-0.98)	0.95 (0.92-0.98)	0.41
FNFH/MPH	64	0.97 (0.96-0.99)	0.97 (0.95-0.98)	1 (0.98-1)	0.031

Median (25th-75th percentile), gain in height was defined as the difference between final or near- final adult height (FNFH) and baseline predicted adult height, gain in predicted height was defined as the difference between the final predicted adult height and baseline predicted adult height.
MPH: mid-parental height

Table 2A. Treatment duration					
		Treatment duration			
	n	<24 mo (n=24)	24-36 mo (n=31)	>36 mo (n=14)	p value
Gain in height (cm)	69	0.6 (-1.1-3.6)	1 (-3-2.9)	10.7 (0.2-13)	0.005
Gain in predicted height (cm)	68	2 (1-4)	2 (-2-5)	15 (5-17)	<0.001
FNFH-MPH (cm)	65	-5.7 (-10.8 to -2.3)	-5.9 (-7.8 to -3.9)	0.5 (-1.9-4.1)	0.002
Predicted height/MPH	65	0.97 (0.93-0.98)	0.97 (0.96-0.98)	0.96 (0.93-0.98)	0.26
FNFH/MPH	65	0.97 (0.94-0.99)	0.97 (0.96-0.98)	1 (0.99-1.02)	0.001
Median (25 th -75 th percentile)-gain in height was defined as the difference between final or near- final adult height (FNFH) and baseline predicted adult height-gain in predicted height was defined as the difference between the final predicted adult height and baseline predicted adult height. FAH: final adult height, MPH: mid-parental height					
Table 2B. Testicular volume					
		Testicular volume at initiation			
	n	1-3 mL (n=2)	4-8 mL (n=19)	15-25 mL (n=26)	p value
Gain in height (cm)	66	14.1(13-15.1)	4.3 (-1.2-10)	0.2 (-1.8-2.9)	0.012
Gain in predicted height (cm)	65	17 (14-21)	5 (4-11)	1 (-2-4)	<0.001
FNFH-MPH (cm)	61	4.1 (4-4.1)	-5.8 (-7.8-1.1)	-4.6 (-6.9 to -3.9)	0.14
Predicted height/MPH	61	0.95 (0.94-0.95)	0.96 (0.94-0.98)	0.97 (0.97-0.99)	0.12
FNFH/MPH	61	1.02 (1.02-1.02)	0.97 (0.96-1)	0.97 (0.96-0.98)	0.11
Median (25 th -75 th percentile), gain in height was defined as the difference between final or near- final adult height (FNFH) and baseline predicted adult height, gain in predicted height was defined as the difference between the final predicted adult height and baseline predicted adult height. FAH: final adult height, MPH: mid-parental height					
Table 2C. Growth hormone therapy					
	n	GH therapy n=47	No GH therapy n=24	p value	
Gain in height (cm)	71	2.7 (-1.8-6.3)	0.2 (-2.3-1.6)	0.022	
Gain in predicted height (cm)	70	4 (0-10)	2 (0-5)	0.20	
FAH-MPH (cm)	66	-4 (-6.1-0.8)	-7.7 (-10.8 to -4.9)	<0.001	
Predicted height/MPH	66	0.97 (0.945-0.98)	0.97 (0.94-0.98)	0.97	
FAH/MPH	66	0.98 (0.965-1)	0.96 (0.94-0.97)	0.002	
Median (25 th -75 th percentile)-gain in height was defined as the difference between final or near- final adult height (FNFH) and baseline predicted adult height, gain in predicted height was defined as the difference between the final predicted adult height and baseline predicted adult height. FAH: final adult height, MPH: mid-parental height, GH: growth hormone					

Table 3. Testosterone levels					
	n	Overall	Anastrozole n=59	Letrozole n=11	p value
Initial testosterone (ng/dL)	45	218 (89-334)	234 (102-365)	167 (8-190)	0.037
Testosterone at 1 year (ng/dL)	51	546 (272-637)	540 (287-615)	699 (272,-841)	0.20
Testosterone at 2 years (ng/dL)	30	476 (329-605)	438 (285-579)	575 (452-917)	0.18
Final testosterone (ng/dL)	52	495 (355-608)	482 (355-567)	592 (488-821)	0.10
Median (25 th -75 th percentile)					

attain greater adult height compared to those receiving GH alone (7,16). In contrast, Varimo et al. (17) found that two years of letrozole monotherapy in pre- and early-pubertal boys with ISS did not significantly improve adult height compared to placebo. Among boys with GHD, combined GH and anastrozole therapy was associated with improved PAH versus GH alone, particularly with longer treatment durations (6). Similarly, Wickman et al. (18) reported a 5.1 cm increase in PAH among boys with CDGP treated with letrozole compared to placebo or no treatment ($p=0.004$). Neely et al. (19) observed a 4.2 cm increase in PAH with anastrozole in boys with short stature, whereas letrozole showed no significant benefit in the same cohort. In contrast, a retrospective study by Shams et al. (20) found no significant PAH improvement in boys with rapid pubertal progression, bone age ≥ 13 years, and short stature following short-term AI therapy.

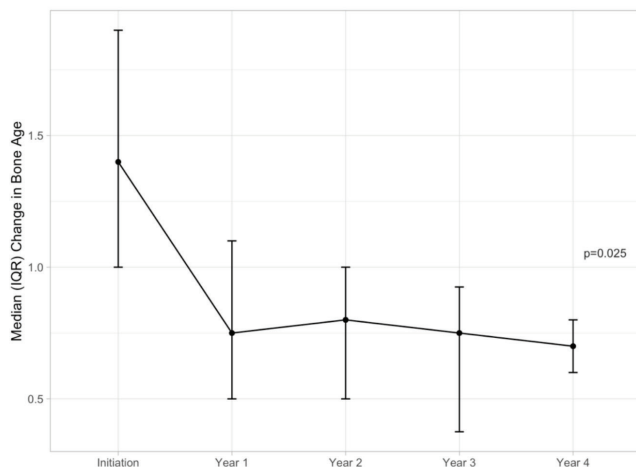
In our study, we assessed the impact of AI therapy on the FNFH of boys with a variety of underlying diagnoses, all of whom had predicted heights below their MPH and ABA. Overall, the gain in height observed was lower than what has been reported in prior studies. However, this may reflect an underestimation, as final adult height data were not available for all subjects with NFH used instead. This interpretation is supported by the more substantial gain in predicted height noted, which was based on patients' final available bone age results.

Since the purpose of AI treatment is to slow down bone age advancement by reducing estrogen, it is important to note that bone age advancement significantly slowed during treatment compared to the period prior to treatment initiation, when the mean bone age advancement was faster than chronological progression. The Bayley-Pinneau method used to calculate the PAH assumes an average bone age advancement and average growth velocity. Patients with a rapidly ABA would likely not reach their PAH as calculated by the above method. Thus, without intervention, patients may have achieved adult heights lower than their baseline PAH, although this remains speculative.

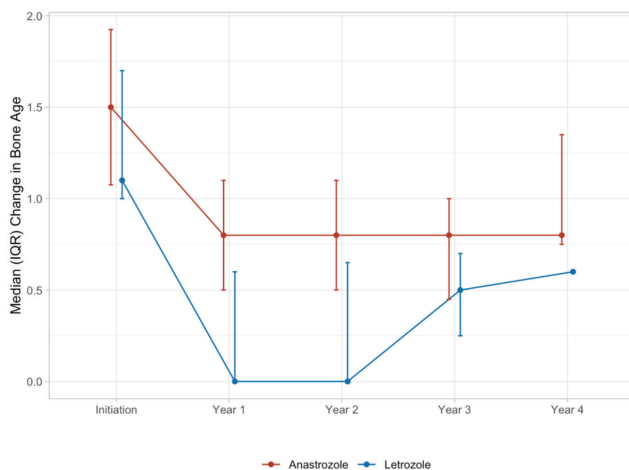
In contrast to the studies by Neely et al. (19) and Zegarra et al. (13), patients in our study who were treated with letrozole achieved a greater gain in height and FNFH closer to their MPH than those treated with anastrozole. This difference persisted even after adjusting for GH therapy. However, it is important to note that there were only eleven subjects in the letrozole group in our study, which was substantially fewer than the anastrozole group (which may introduce bias); thus the statistical difference between the two groups for gain in height must be interpreted with caution. This smaller sample size reflects the fact that letrozole has largely fallen out of favor in our clinical practice due to safety concerns, including reports of spinal deformities and a more pronounced decline in BMD Z-scores compared to anastrozole (13,14).

Consistent with previous studies, longer duration of treatment was associated with greater gain in height and a FNFH closer to MPH. Our study also showed that initiation of treatment at earlier stages of puberty (testicular volume ≤ 8 mL) resulted in greater gains in height, which is likely due to the substantial increase in testosterone production as puberty progresses. Moreover, concurrent treatment with GH was associated with a significantly higher median gain in height.

While prior studies have focused on the effect of AI therapy on height outcomes of patients treated for specific diagnoses including ISS, GHD or CDGP, our study included a broader patient population with a variety of diagnoses including the above as well as SGA, overweight/obesity, CAH, premature adrenarche and early puberty. No significant differences in the



a)



b)

Figure 1. Change in bone age over time. a) Overall median change in bone age over time. b) Median change in bone age over time in the two treatment groups.

treatment outcomes were observed based on the underlying diagnosis.

Adverse effects were generally mild. Acne was the most commonly reported side effect. Mental health concerns were evaluated and noted in 8.5% of the patients, though it is unclear whether systematic mental health screening was performed at follow up visits. Laboratory monitoring revealed increased testosterone levels and mild elevations of liver function tests, which mostly resolved on repeat testing, with no significant difference between the two treatment groups. This contrasts prior studies that reported greater testosterone increases with letrozole compared to anastrozole (13,19). Patients in our study did not undergo DXA scans during or after treatment with AIs, so the impact on BMD Z-scores remains unknown.

Study Limitations

Limitations of our study include the study design as a retrospective chart review with limited control over available data, particularly on the final adult height of patients included. Another limitation is the relatively small sample size, particularly in the letrozole group, though the sample was larger than in several prior studies on this topic.

Conclusion

This study supports the efficacy of AI therapy and particularly letrozole in improving the final adult height of males with compromised PAH and ABA, irrespective of the underlying

diagnosis. Patients treated with letrozole, at earlier pubertal stages, for longer duration and receiving concurrent treatment with GH attained better final height outcomes. Nonetheless, concerns about the safety of use persist, particularly regarding their potential impact on bone health.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Weill Cornell Medicine Research Integrity IRB and determined to qualify for exemption per the Code of Federal Regulations on the Protection of Human Subjects (WRG submission number: 23-08026421-02, FWA number: FWA00000093, date: 28/12/2023).

Informed Consent: Given the retrospective design, the requirement for informed consent was waived.

Footnotes

Presented in: Part of the content of this manuscript was previously presented as a poster presentation at the Pediatric Endocrine Society Annual Meeting (PES 2025, National Harbor, MD).

Authorship Contributions

Concept: Athanasia Bouliari, Oksana Lekarev, Karen Lin-Su Design: Athanasia Bouliari, Karen Lin-Su, Data Collection or Processing: Athanasia Bouliari, Analysis or Interpretation: Athanasia Bouliari,

Anjile An, Karen Lin-Su, Literature Search: Athanasia Bouliari, Karen Lin-Su Writing: Athanasia Bouliari, Oksana Lekarev, Karen Lin-Su.

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