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Research Article

The Efficacy of Anastrozole and Growth Hormone Therapy on Adult Height in Six Adolescent Males with Growth Hormone Deficiency or Idiopathic Short Stature

Serife Uysal, Juanita K. Hodax, Lisa Swartz Topor, and Jose Bernardo Quintos

Division of Pediatric Endocrinology, Rhode Island Hospital and Warren Alpert School of Brown University, Providence, RI, USA

Correspondence should be addressed to Jose Bernardo Quintos; jbquintos@brown.edu

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Background. Data on adult height outcomes of the use of Anastrozole and Growth Hormone (GH) in pubertal males with Growth hormone deficiency (GHD) and Idiopathic short stature (ISS) are limited. *Objective*. We examined the effect of Anastrozole and GH therapy on near adult height (NAH) with pubertal males with GHD or ISS. *Methods*. Retrospective review of 419 charts from 2008 to 2015. The primary outcomes are NAH compared to mid-parental target height (MPTH) and predicted adult height (PAH). *Results*. We identified 23 patients (5 SGA/IUGR, 1 Noonan syndrome, 6 GHD, and 11 ISS). Six patients (4 GHD; 2 ISS) achieved NAH. Prior to Anastrozole treatment, the mean chronological age was 13.9 ± 0.2 years (range 13.7–14.4), bone age was 13.6 ± 0.6 years (range 12.5–14), mean height SDS was −1.5 ± 0.5 (range −0.8 to −2.3), and mean PAH was 162.6 ± 5.9 cm (range 153.5–168.6). MPTH was 173.6 cm ± 7 (range 161.8–181.6). Patients received Anastrozole for an average of 30.5 months (range 19–36 months). At NAH, the mean chronological age was 16.7 ± 0.8 years (range 15.9–18.1 years) and height was 170 ± 1.8 cm (range 168.5–173.4 cm). The mean height SDS improved to +0.81 ± 0.6 (range +0.08 to +1.92, $p = 0.002$). Net height gain was 7.3 cm compared to pretreatment PAH ($p < 0.01$) and overall the mean adult height remained 3.5 cm below MPTH. *Conclusion*. Anastrozole and GH therapy can be effective in augmenting adult height without significant side effects. However, the long-term safety and efficacy of aromatase inhibitor use in pediatrics remain limited.

1. Background

Approximately 17% of adult male height and 12% of adult female height result from the pubertal growth spurt [1]. Maximizing the pubertal growth spurt in children with growth hormone deficiency (GHD) or idiopathic short stature (ISS) is challenging due to limited time available for linear growth. Different modalities to increase the adult height in pubertal adolescents with GHD and ISS include high dose GH therapy, gonadotropin releasing hormone analogs, and more recently aromatase inhibitors (AI) [2].

AI block the aromatase enzyme, which prevents conversion of testosterone to estrogen, delays closure of the epiphyses, and may prolong the time period for pubertal growth. The identification of one male with a point mutation in the estrogen receptor gene [3] and another male with a point mutation in the aromatase enzyme gene [4, 5] confirmed that estrogen is the principal hormone causing epiphyseal closure. Studies involving AI in male patients with constitutional delay of growth and puberty [6, 7], ISS [8, 9], and GHD [10] suggest that AI can delay bone age acceleration and increase predicted adult height (PAH). However, data regarding adult height outcomes are limited [6–12].

In the current study, we reviewed growth and height outcomes for six male adolescents with GHD or ISS treated with GH therapy to determine whether Anastrozole improves the adult height above the pretreatment PAH.

2. Methods

This is a retrospective chart review of male patients between 12 and 18 years of age who were seen at the pediatric endocrinology clinic at Rhode Island Hospital from January 2008 to July 2015. We identified patients between 12 and 18

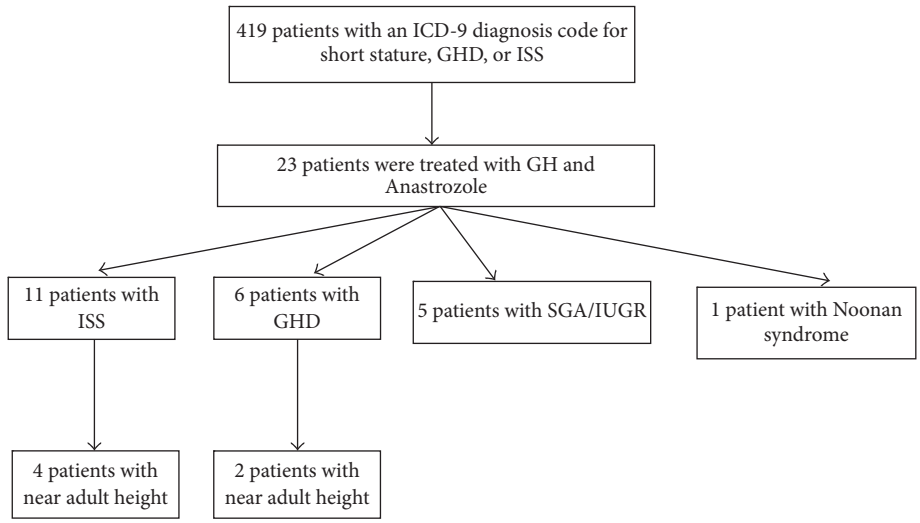

Figure 1: Study population.

years who had International Classification of Disease Ninth (ICD-9) and Tenth (ICD-10) diagnosis codes for short stature (ICD-9 783.43 and ICD-10 R62.52), GHD (ICD-9 253.3 and ICD-10 E34.3), or ISS (ICD-9 783.43 and ICD-10 R62.52). We identified 419 patients with those diagnoses. We reviewed the charts of these patients to identify those treated with Anastrozole in addition to GH therapy. We identified 23 patients with a diagnosis of short stature, GHD, or ISS and treatment with GH and Anastrozole. The following inclusion criteria were applied to these patients:

(a) GHD was defined as either (i) short stature characterized by a height less than 2 standard deviations below the mean height for chronological age and sex [13] or (ii) poor growth (growth velocity ≤ 25 percentile) [14] of corresponding chronological age or (iii) peak GH responses to GH provocative test with two different pharmacological stimuli ≤ 5.5 ng/mL measured by immunochemiluminometric assay (ICMA).

(b) ISS was defined as (i) short stature characterized by a height less than 2 standard deviations below the mean height for chronological age and sex without endocrine, metabolic, nutritional, or chromosomal abnormalities and (ii) peak GH responses to GH provocative test with two different pharmacological stimuli > 5.5 ng/mL measured by ICMA.

(c) Patients were excluded if short stature was due to nutritional, metabolic, or chromosomal abnormalities or due to being born small for gestational age/intrauterine growth retardation (SGA/IUGR).

Out of 23 patients treated with Anastrozole and GH, excluded patients included 5 who were born with SGA/IUGR and 1 with Noonan syndrome. Of the remaining 17 patients, we identified 6 patients (2 with GHD and 4 with ISS) who received GH and Anastrozole and achieved near adult height (NAH). Figure 1 summarizes the study population. All patients received Anastrozole 1 mg daily based on Mauras et al.'s clinical trial [10]. NAH was defined as growth velocity less than 2.5 cm per year or bone age ≥ 15 years in a fully pubertal male. Anthropometric measures were obtained using digital scales and Harpenden stadiometer. Bone age X-ray was assessed based on the method of Greulich and Pyle [15]. One pediatric endocrinologist read all bone age studies. Pubertal stage was assessed by physical examination according to Tanner's criteria [16]. Tanner staging was performed by one pediatric endocrinologist. Outcome measures were pretreatment PAH, height, and height SDS, and posttreatment height SDS and NAH. PAH was calculated using the method of Bayley and Pinneau [17]. Rhode Island Hospital Institutional Research Board approved the study.

2.1. Assays. Serum concentrations of testosterone, LH, FSH, and estradiol were measured at baseline and annually at Esoterix Laboratory Services, Calabasas Hills, California. Serum LH and FSH were measured by chemiluminescent assay. Serum testosterone was measured by liquid chromatography with isotope dilution mass spectrometry detection after supported liquid extraction. Analysis was performed using high-pressure liquid chromatography separation with tandem mass spectrometric detection (LC-MS/MS). Testosterone stable labelled isotope was added as internal standard to all sample and standard aliquots. The samples were extracted, evaporated, reconstituted, and then injected onto an LC-MS/MS system. A triple quadrupole mass spectrometer was used for detection. The amount of testosterone in each sample was calculated from a linear plot generated by purified testosterone standards ranging from 2.5 to 5000 ng/dL. Serum estradiol was measured using two-dimensional liquid chromatography (HPLC) with tandem mass spectrometry detection after liquid-liquid extraction. Carbon-13 labelled DL-estradiol was added to serum aliquots to evaluate and correct for recovery of the estradiol from each sample. Extract supernatants from samples and standards were separated, dried, and reconstituted. A triple quadrupole mass spectrometer was used for detection. The amount of

Table 1: Baseline clinical characteristics of study patients before initiation of GH therapy.

Patient #	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Mean
Diagnosis	ISS	GHD	ISS	ISS	ISS	GHD	N/A
Chronological age (yr)	13.0	9.6	13.1	12.4	13.9	8.0	11.7 ± 2.3
Bone age (yr)	11.5	10	10	13	14	6	10.7 ± 2.8
Height (cm)	139.5	123	136.6	135.1	145.2	112.6	132 ± 11.9
Height SDS	−2.1	−2.2	−2.6	−2.3	−2.2	−2.7	−2.3 ± 0.24
Weight (kg)	34.9	26.9	31	35.2	36.5	19.9	30.7 ± 6.3
Weight SDS	−1.4	−0.9	−2.3	−1.0	−1.9	−1.9	−1.6 ± 0.5
Body Mass Index (kg/m^2)	17.9	17.7	16.6	19.2	17.3	15.7	17.4 ± 1.1
BMI SDS	−0.2	−0.5	−0.9	0.4	−0.8	−0.04	−0.16 ± 0.6
Growth velocity (cm/yr)	6.3	3	2.6	N/A	5.1	4	4.2 ± 1.5
Peak GH level (ng/mL)	7.9	4.5	9.2	N/A	N/A	3.2	N/A
Tanner stage							
Pubic hair	2	1	2	1	3	1	N/A
Genitalia	2	1	2	1	3	1	N/A
Testicle size (cc)	6–8	3	6	3	10	2-3	N/A
PAH (cm)	165.6	156.5	167.4	154.9	157.5	162	160.6 ± 4.6
MPTH (cm)	181.6	161.8	170.3	179.2	174.1	174.6	173.6 ± 7
MPTH SDS	0.7	−2.0	−0.9	0.3	0.4	−0.3	−0.3 ± 1

estradiol in each sample was calculated from a linear plot generated by purified estradiol standards ranging from 1.0 to 500 pg/mL.

2.2. Statistical Analysis. The primary endpoint of this study was NAH compared to pretreatment PAH and mid-parental target height (MPTH). Continuous variables were reported as mean with standard deviation and median with ranges. Treatment group differences were evaluated with two-sampled t-test with equal variance. A p value of less than 0.05 was considered statistically significant.

3. Results

3.1. Clinical Characteristics before Initiation of GH. Table 1 summarizes the baseline characteristics of each patient before initiation of GH therapy. Mean chronological age was 11.7 ± 2.3 years (range 8 to 13.9) and bone age was 10.7 ± 2.8 years (range 6 to 14). Mean height SDS was −2.3 ± 0.24 (range −2.1 to −2.7) and mean MPTH SDS −0.3 ± 1 (range −2 to +0.7). Mean annualized growth velocity was 4.2 ± 1.5 cm (range 2.6 to 6.3) per year. Baseline annualized growth velocity was not available for one patient. Half of the patients were prepubertal and half were pubertal. Mean PAH was 160.6 ± 4.6 cm (range 154.9 to 165.6) compared to mean MPTH of 173.6 ± 7 cm (range 161.8 to 181.6).

3.2. Clinical Characteristics before Initiation of Anastrozole. Mean chronological age was 13.9 ± 0.27 years (range 13.7 to 14.4) and bone age was 13.6 ± 0.6 years (range 12.5 to 14). Mean height SDS was −1.5 ± 0.5 (range −0.8 to −2.3). Mean PAH was 162.6 ± 5.9 cm (range 153.5 to 168.6) compared to mean MPTH of 173.6 ± 7 cm (range 161.8 to 181.6). Mean annualized growth velocity was 9.3 ± 3.1 cm per year (range 5 to 12.7). Patients had a mean testicular volume 13.6 mL (range 10–20 mL). Median duration of GH therapy before initiation of Anastrozole was 14.5 months. The GH dose for all patients ranged from 0.22 to 0.36 mg/kg/week. Table 2 compares the baseline characteristics of each patient before and after Anastrozole treatment.

3.3. Near Adult Height. At NAH, the mean chronological age was 16.7 ± 0.8 years (range 15.9 to 18.1) and mean bone age was 15.5 ± 1.6 years (range 14 to 17). The mean NAH was 170 ± 1.8 cm (range 168.5 to 173.4) compared to mean MPTH of 173.6 ± 7 cm (range 161.8 to 181.6). Five out of 6 patients exceeded their pretreatment PAH and patients numbers 2 and 3 exceeded their MPTH. Figure 2 compares the NAH of each patient with MPTH and PAH before the initiation of Anastrozole treatment. The mean net height gain was 7.3 cm (range −0.1 to +15.4) compared to pretreatment PAH ($p < 0.01$), and the mean height SDS improved to +0.81 ± 0.6 (range +0.08 to +1.92, $p = 0.002$). Figure 3 compares the height SDS before and after Anastrozole treatment. Patients received Anastrozole for median duration of 30.5 months (range 19–36). Overall the mean NAH was 3.5 ± 8.2 cm below their mean MPTH. All patients continued GH therapy while they were receiving Anastrozole.

3.4. Safety Issues. All patients tolerated Anastrozole well and no patients report any side effects of Anastrozole including nausea, vomiting, abdominal pain, back pain, mood changes, or hot flashes. Endocrine evaluation including serum testosterone, LH, and FSH were followed periodically and were within normal limits. Table 3 summarizes the most recent available laboratory evaluation.

Table 2: Comparison of clinical characteristics of patients before and after Anastrozole treatment.

	Prior to Anastrozole	At NAH
Chronological age (yr)	13.9 ± 0.27 (range 13.7 to 14.4)	16.7 ± 0.8 (range 15.9 to 18.1)
Bone age (yr)	13.6 ± 0.6 (range 12.5 to 14)	15.5 ± 1.6 years (range 14 to 17)
Height (cm)	150.7 ± 4.5 (range 142.6 to 156.3)	170 ± 1.8 cm (range 168.5 to 173.4)
Height SDS	−1.55 ± 0.5 (range −0.8 to −2.3 SD)	−0.74 ± 0.2 (range −0.4 to – 1.1)
Tanner stage		
Pubic hair	2–4	4-5
Genitalia	3–5	4-5
Testicle size (mL)	10–20	20–25
PAH (cm)	162.6 ± 5.9 (range 153.5 to 168.6)	N/A
MPTH (cm)	173.6 ± 7 (range 161.8 to 181.6)	173.6 ± 7 (range 161.8 to 181.6)

Table 3: Available laboratory data at NAH.

	Testicle size (cc)	LH (mIU/mL)	FSH (mIU/mL)	Testosterone (ng/dL)	Estradiol (pg/mL)	IGF 1 (ng/mL)
Patient 1	25	5.1	N/A	734	18	410
Patient 2	25	2.8	14	523	3	534
Patient 3	>25	1.6	3.8	343	N/A	301
Patient 4	25	1.9	14	446	7.6	578
Patient 6	20–25	3.8	14	598	N/A	304

Laboratory data at NAH was not available for Patient 5.

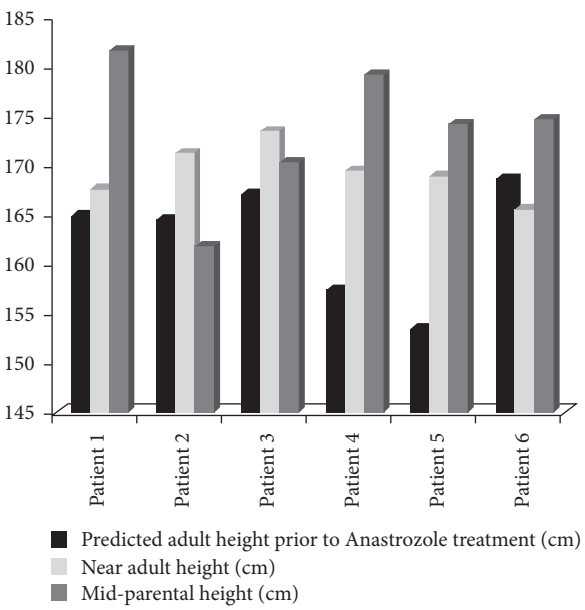

Figure 2: Patients with near adult height comparing to predicted adult height prior to Anastrozole treatment and mid-parental height.

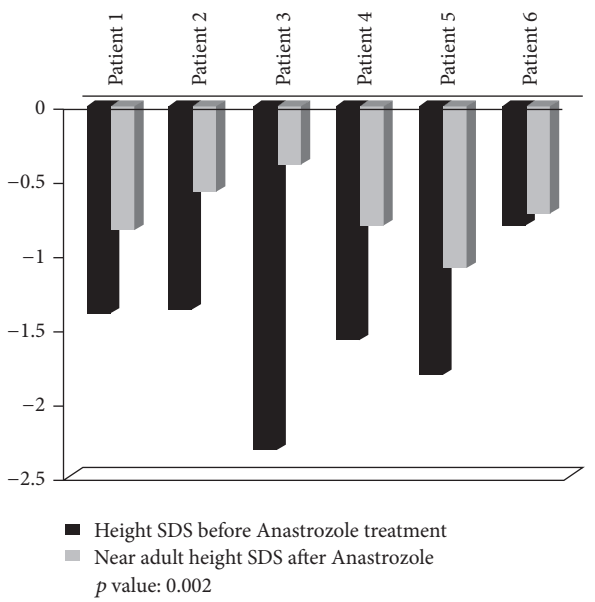

Figure 3: Comparison of height SDS before and after Anastrozole treatment.

4. Discussion

Our study showed that the use of Anastrozole in addition to GH therapy resulted in a statistically significant increase in NAH compared to pretreatment PAH in boys with ISS or GHD. The delay in the tempo of bone age acceleration caused by aromatase inhibition and decreased estrogen resulted in a significant net gain in height. Overall our cohort achieved a mean net height gain of 7.3 cm compared to pretreatment PAH. However the mean NAH remained 3.5 cm below the mean MPTH.

Initial use of AI was studied in children with constitutional delay of puberty. Wickman et al. demonstrated a 5.1 cm mean height gain compared to the pretreatment PAH in children with constitutional delay of puberty who were

treated with AI for twelve months, in combination with low dose testosterone therapy for 6 months [6]. The same subjects were followed until near final height [7] and the boys treated with AI attained a mean NAH 6.7 cm higher compared to the control group.

Subsequent studies were done in patients with ISS and GHD [8, 10, 11]. Hero et al. [8] in a prospective double-blinded, randomized, placebo controlled study showed that subjects with ISS treated with Letrozole have an increased PAH by 5.9 cm and height SD score for bone age increased by 0.7 SD score. Mauras et al. in a double-blinded [10], randomized, placebo controlled clinical trial observed a net increase in PAH of 4.5 ± 1.2 cm after 2 years and 6.7 ± 1.4 cm after 3 years of treatment with Anastrozole. In this study, safety data including glucose and lipid profile were similar between groups. The investigators observed that the patients who received Anastrozole in addition to GH therapy had significant delay in bone age advancement, which resulted in statistically significant net gain in PAH.

Also Rothenbuhler et al. [11] conducted a prospective randomized study to compare GH alone and GH and Anastrozole in 24 adolescent boys with ISS who achieved NAH. Height gain compared to the pretreatment PAH was +4.6 cm greater and height SDS at NAH was +0.7 SD score greater in the subjects treated with GH and Anastrozole compared to the GH alone group. More recently, Mauras et al. [9] in a randomized trial of 3-arm comparator study using AI, GH, and combination of AI and GH demonstrated that combination treatment increased linear growth significantly from baseline when used for 2-3 years. At near adult height the absolute change in height SDS from baseline was +0.8 in AI, +1.0 in GH, and +1.3 in GH/AI. The height SDS at near adult height was −1.4 ± 0.1 in AI group, −1.4 ± 0.2 in GH group, and −1.0 ± 0.1 in AI/GH group. The subjects tolerated the AI well without significant side effects. Despite the limited number of subjects and lack of control group, the study showed positive results using AI/GH in augmenting the final height. The mean height SDS at baseline in our study was similar to Mauras's study; however the PAH in our study was more compromised compared to their MPTH. Despite small number of patients in our study, our findings provide additional evidence of potential benefit of AI in augmenting adult height.

Limitations of our study include a small sample size, lack of control group, heterogeneous nature of the patients, and retrospective study design. However, the results of our study are consistent with the previous studies of the efficacy of Anastrozole in augmenting adult height. Larger prospective, randomized, controlled clinical trials are needed to evaluate the efficacy and safety of AI in children with ISS and GH deficiency in augmenting adult height.

In summary, Anastrozole in addition to GH increased adult height significantly compared to pretreatment PAH in this small cohort of boys with ISS or GHD. This suggests that Anastrozole therapy is effective in augmenting adult height without significant side effects during therapy. However, the long-term safety and efficacy of aromatase inhibitors in boys with GH deficiency and ISS remains limited and further investigation is needed.

Conflicts of Interest

None of the authors have potential, perceived, or real conflicts of interest to disclose.

References

[1] J. P. Bourguignon, "Linear growth as a function of age at onset of puberty and sex steroid dosage: therapeutic implications," *Endocrine Reviews*, vol. 9, no. 4, pp. 467–488, 1988.

[2] N. Mauras, "Strategies for maximizing growth in puberty in children with short stature," *Endocrinology and Metabolism Clinics of North America*, vol. 38, no. 3, pp. 613–624, 2009.

[3] E. P. Smith, J. Boyd, G. R. Frank et al., "Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man," *The New England Journal of Medicine*, vol. 331, no. 16, pp. 1056–1061, 1994.

[4] C. Carani, K. Qin, M. Simoni et al., "Effect of testosterone and estradiol in a man with aromatase deficiency," *The New England Journal of Medicine*, vol. 337, no. 2, pp. 91–95, 1997.

[5] A. Morishima, M. M. Grumbach, E. R. Simpson, C. Fisher, and K. Qin, "Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens," *The Journal of Clinical Endocrinology & Metabolism*, vol. 80, no. 12, pp. 3689–3698, 1995.

[6] S. Wickman, I. Sipilä, C. Ankarberg-Lindgren, E. Norjavaara, and L. Dunkel, "A specific aromatase inhibitor and potential increase in adult height in boys with delayed puberty: a randomised controlled trial," *Lancet*, vol. 357, no. 9270, pp. 1743–1748, 2001.

[7] M. Hero, S. Wickman, and L. Dunkel, "Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty," *Clinical Endocrinology*, vol. 64, no. 5, pp. 510–513, 2006.

[8] M. Hero, E. Norjavaara, and L. Dunkel, "Inhibition of estrogen biosynthesis with a potent aromatase inhibitor increases predicted adult height in boys with idiopathic short stature: a randomized controlled trial," *The Journal of Clinical Endocrinology & Metabolism*, vol. 90, no. 12, pp. 6396–6402, 2005.

[9] N. Mauras, J. L. Ross, P. Gagliardi et al. et al., "Randomized trial of aromatase inhibitors, growth hormone or combination in pubertal boys with idiopathic short stature," *The Journal of Clinical Endocrinology & Metabolism*, vol. 101, no. 12, pp. 4984–4993, 2016.

[10] N. Mauras, L. Gonzalez de Pijem, H. Y. Hsiang et al., "Anastrozole increases predicted adult height of short adolescent males treated with growth hormone: a randomized, placebo-controlled, multicenter trial for one to three years," *The Journal of Clinical Endocrinology & Metabolism*, vol. 93, no. 3, pp. 823–831, 2008.

[11] A. Rothenbuhler, A. Linglart, and P. Bougneres, "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," *International Journal of Pediatric Endocrinology*, vol. 2015, no. 1, article 4, 2015.

[12] J. A. Ferris and M. E. Geffner, "Are aromatase inhibitors in boys with predicted short stature and/or rapidly advancing bone age effective and safe?" *Journal of Pediatric Endocrinology and Metabolism*, vol. 30, no. 3, pp. 311–317, 2017.

[13] R. J. Kuczmarski, C. L. Ogden, L. M. Grummer-Strawn et al., "CDC growth charts: United States," *Advance Data*, no. 314, pp. 1–27, 2000.

[14] J. M. Tanner and P. S. W. Davies, "Clinical longitudinal standards for height and height velocity for North American children," *The Journal of Pediatrics*, vol. 107, no. 3, pp. 317–329, 1985.

[15] W. W. Greulich and S. I. Pyle, *Radiographic Atlas of Skeletal Development of the Hand and Wrist*, Stanford University Press, Stanford, Calif, USA, 2nd edition, 1959.

[16] J. M. Tanner, *Growth at Adolescence; With a General Consideration of the Effects of Hereditary and Environmental Factors upon Growth and Maturation from Birth to Maturity*, Blackwell Scientific Publications, Springfield, Ill, USA, 2nd edition, 1962.

[17] N. Bayley and S. R. Pinneau, "Tables for predicting adult height from skeletal age: revised for use with the greulich-pyle hand standards," *The Journal of Pediatrics*, vol. 40, no. 4, pp. 423–441, 1952.