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Efficacy and Safety of Aromatase Inhibitor Combined with Growth Hormone in Korean Boys with Idiopathic Short Stature: A Retrospective Study

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Abstract

Aromatase inhibitors (AIs) have been suggested as adjuncts to delay skeletal maturation and extend growth potential in boys with idiopathic short stature (ISS), but evidence in Asian populations remains scarce. This study evaluated the safety and efficacy of growth hormone (GH) and aromatase inhibitor (AI) combination therapy in Korean boys with ISS. We retrospectively analyzed 35 Korean boys with ISS treated between June 2023 and May 2025 at a single center. The GH + AI group was significantly older and had more advanced bone age than the GH-only group. The GH + AI group, which had a more advanced bone age at baseline, achieved an annual growth velocity of 5.21 ± 1.61 cm/year, whereas the younger GH-only group grew at 10.25 ± 2.54 cm/year. Despite the slower growth rate, bone maturation was significantly delayed in the GH + AI group, indicating preserved growth potential. Both groups exhibited significant increases in insulin-like growth factor 1 and insulin-like growth factor-binding protein 3, with higher levels in the GH + AI group than in the GH-only group at the last visit. Mild adverse events were reported without treatment discontinuation. GH + AI combination therapy may represent a safe and effective alternative for Korean boys with ISS and advanced bone age, particularly in late puberty when growth potential is limited.

Keywords

Idiopathic Short Stature, Aromatase Inhibitor, Growth Hormone, Pubertal Growth, Off-Label Therapy

1. Introduction

Idiopathic short stature (ISS) in boys is an important clinical concern owing to the psychosocial impact of short stature and the limitations of growth hormone (GH) monotherapy in cases of rapidly advancing bone age [1] [2]. Aromatase inhibitors (AIs) have been proposed as adjuvant treatments that can inhibit estrogen production to delay bone maturation and extend the growth period [2]-[4].

P450 aromatase is a key enzyme in converting C19 androgens (androstenedione and testosterone) to C18 estrogens (estrone and estradiol) [5]. In males, testicular aromatase contributes to only a small proportion (approximately 15%) of circulating estrogens, while extragonadal tissues, e.g., bone, brain, and adipose tissue, play a critical role in local estrogen synthesis [6] [7]. This extragonadal estrogen production acts mainly through paracrine and intracrine mechanisms, regulating skeletal maturation and epiphyseal fusion [8] [9].

The importance of estrogen in male bone development is evident in cases where delayed closure of the epiphysis and large final elongation are observed in patients with estrogen receptor gene mutations or aromatase deficiency [10] [11]. Conversely, rapid progression of bone age and low final elongation have been reported in cases of aromatase excess syndrome, suggesting that estrogen plays a decisive role in bone maturation [12]. Based on this mechanism, AIs have been proposed as adjuncts to GH therapy to suppress estrogen production, delay bone maturation, and prolong the growth period in boys with ISS.

Several clinical studies have reported the effects of AI on height increase in boys with ISS [13]-[15]. In one randomized placebo-controlled study, when letrozole was administered for 2 years, the progression of bone age was significantly suppressed and the predicted final height increased by 5.9 cm, with no negative effect on bone density [16]. In another study, the combination of GH and AI showed better height increase and improvement in body composition change than GH alone or AI alone [17]. However, concerns remain regarding potential adverse effects, including glucose intolerance, hematologic changes, acne, and liver function abnormalities, which warrant careful evaluation in clinical practice [18]-[20].

Most existing studies on the use of AIs in patients with ISS have been conducted in Western populations. Thus, clinical data from Asian patients, particularly Korean children, remain limited. In Korea, the use of AIs for ISS is not officially approved, and clinicians often hesitate to use this treatment owing to the absence of evidence in Asians. Therefore, this study aimed to evaluate the short-term efficacy and safety of combined GH and AI therapy in Korean boys with ISS and its effect on advanced bone age, with the goal of providing the first clinical evidence for this treatment approach in an Asian population.

2. Materials and Methods

2.1. Use of Artificial Intelligence

Language editing assistance was provided by ChatGPT (OpenAI, San Francisco, CA, USA) to improve grammar and clarity. All artificial intelligence-generated suggestions were reviewed and revised by the authors for accuracy and style.

2.2. Ethics Statement

This study was approved as exempt from full review by the Public Institutional Review Board (IRB) designated by the Ministry of Health and Welfare, Korea (IRB number: P01-202507-01-073). The requirement for informed consent was waived because of the retrospective study design and use of anonymized patient data.

2.3. Study Design and Population

This retrospective cohort study was performed to evaluate the short-term efficacy and safety of AI combined with GH therapy in Korean boys with ISS. The medical records of boys treated at a single regional general hospital in Korea between June 2023 and May 2025 were reviewed.

Boys with idiopathic short stature (ISS) were included and divided into two groups: those receiving GH monotherapy and those treated with GH in combination with an AI (letrozole, 2.5 mg/day).

ISS was defined as a height below −2.0 standard deviation score (SDS) for age and sex, normal results on growth hormone stimulation tests, and the absence of systemic, endocrine, or chromosomal disorders that could affect growth.

The allocation of patients to either treatment group was determined by clinical judgment rather than randomization. GH + AI combination therapy was considered for boys who had reached late puberty (Tanner stage ≥ III) and exhibited advanced bone age or limited residual growth potential, whereas GH monotherapy was used for younger boys in earlier pubertal stages or with less advanced bone age.

Patients were excluded if they had chronic illness, chromosomal abnormalities, previous treatment with sex steroids, or were lost to follow-up.

2.4. Treatment Protocol

GH was administered subcutaneously at a dosage of 0.3 mg/kg/week in all patients. In the combination group (GH + AI group), letrozole (2.5 mg) was initiated concurrently with GH and administered orally once daily at bedtime. The treatment duration ranged from 4 - 18 months.

2.5. Data Collection

Baseline and follow-up data were collected, including chronological age, bone age (assessed by the Tanner-Whitehouse 3 method), height, height standard deviation score, and laboratory parameters. Insulin-like growth factor 1 (IGF-1) and insulin-like growth factor-binding protein 3 (IGF-BP3) levels were measured at treatment initiation and the last follow-up. Adverse events, including hair loss, acne, and hematologic abnormalities (e.g., leukopenia and anemia), were recorded. The hemoglobin A1c (HbA1c) level was monitored to ensure metabolic safety.

2.6. Statistical Analysis

No a priori sample size calculation was performed because this was a retrospective study and all eligible patients who met the inclusion criteria during the study period were included. Descriptive statistics were calculated for baseline characteristics and outcome measures. The normality of continuous variables was assessed using the Shapiro-Wilk test, and between-group comparisons were performed using the independent t-test or Mann-Whitney U test, as appropriate. Categorical variables were analyzed using the chi-square test. The paired t-test or Wilcoxon signed-rank test was used to compare pre-treatment and post-treatment outcomes. Statistical significance was set at $p < 0.05$, and all statistical analyses were performed using SPSS (version 26.0; IBM Corp., Armonk, NY, USA).

3. Results

A total of 35 boys with ISS were included in this study, with 8 in the GH-only group and 27 in the GH + AI group. Compared with the GH-only group, the GH + AI group had significantly more advanced bone age at the start of treatment (15.99 ± 1.06 years versus [vs.] 12.38 ± 0.83 years), and their chronological age and height were higher (**Table 1**).

Table 1. Baseline characteristics of the study participants.

Variable	GH-only (mean ± SD)	GH+AI (mean ± SD)
Chronological age (years)	12.08 ± 0.69	14.13 ± 1.17
Bone age (years)	12.38 ± 0.83	15.99 ± 1.06
Height (cm)	146.97 ± 5.34	164.48 ± 4.22
Predicted adult height (cm)	167.50 ± 2.56	166.61 ± 3.87
Midparental height (cm)	171.44 ± 2.62	172.09 ± 3.72

SD, standard deviation; GH, growth hormone; AI, aromatase inhibitor.

Despite these less favorable baseline characteristics, the GH + AI group achieved an annual growth velocity of 5.21 ± 1.61 cm/year, which was statistically lower than that in the GH-only group (10.25 ± 2.54 cm/year, $p = 0.001$) but still clinically meaningful, as reflected by the greater improvement in height SDS compared with the GH-only group (**Table 2**, **Figure 1** and **Figure 2**). Additionally, the GH + AI group demonstrated a significantly lower ΔBA/CA ratio than the GH-only group (0.11 ± 0.25 vs. 0.55 ± 0.64, $p = 0.046$), indicating effective deceleration of bone maturation through aromatase inhibition (**Figure 3**).

IGF-1 and IGF-BP3 levels increased significantly in both groups during treatment. At the end of the treatment period, the IGF-1 level was significantly higher in the GH + AI group than in the GH-only group (728.08 ± 143.45 ng/mL vs. 343.00 ± 67.28 ng/mL, $p = 0.002$). HbA1c levels remained stable in both groups throughout the treatment period.

Table 2. Treatment outcomes.

Outcome Variable	GH-only (mean ± SD)	GH + AI (mean ± SD)	p-value
Annual growth velocity (cm/year, auto-calculated)	10.25 ± 2.54	5.21 ± 1.61	0.001 (t-test)
Height SDS (auto-calculated)	−0.48 ± 0.89	0.31 ± 0.91	0.048 (t-test)
ΔBone age/chronological age ratio (auto-calculated)	0.55 ± 0.64	0.11 ± 0.25	0.046 (Mann-Whitney U test)
IGF-1 level (baseline)	255.00 ± 87.14	535.78 ± 220.26	-
IGF-1 level (last visit)	343.00 ± 67.28	728.08 ± 143.45	0.002 (Mann-Whitney U test)
IGF-BP3 level (baseline)	4764.38 ± 645.00	5444.26 ± 660.65	-
IGF-BP3 level (last visit)	5032.50 ± 974.22	5497.42 ± 702.05	0.417 (t-test)
HbA1c level (baseline)	5.06 ± 0.22	5.21 ± 0.25	-
HbA1c level (last visit)	5.35 ± 0.19	5.28 ± 0.23	0.545 (t-test)

GH, growth hormone; AI, aromatase inhibitor; SDS, standard deviation score; IGF-1, insulin-like growth factor 1; IGF-BP3, insulin-like growth factor-binding protein 3; HbA1c, glycated hemoglobin.

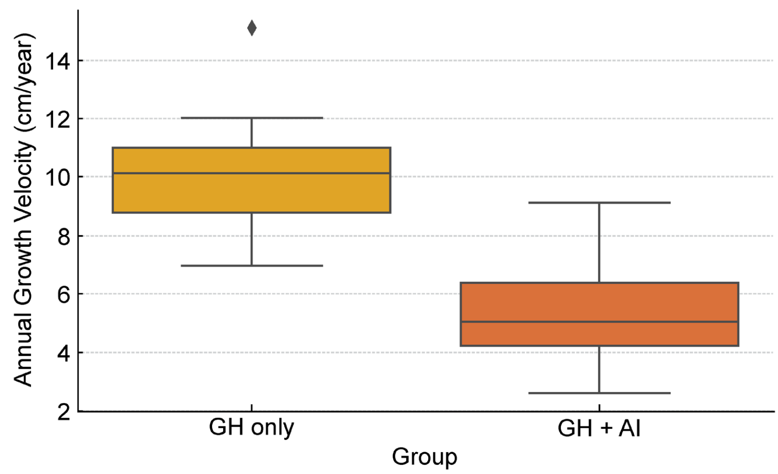

Figure 1. Annual growth velocity (cm/year) in the GH-only and GH + AI groups. Despite a significantly higher annual growth velocity in the GH-only group (p = 0.001), the GH + AI group still exhibits a clinically meaningful annual growth rate, considering their advanced baseline bone age. GH, growth hormone; AI, aromatase inhibitor.

Adverse events were mild and included acne and hair loss (Table 3). None of the participants discontinued treatment due to side effects, and the overall incidence of adverse reactions did not differ significantly between the groups (all $p > 0.05$).

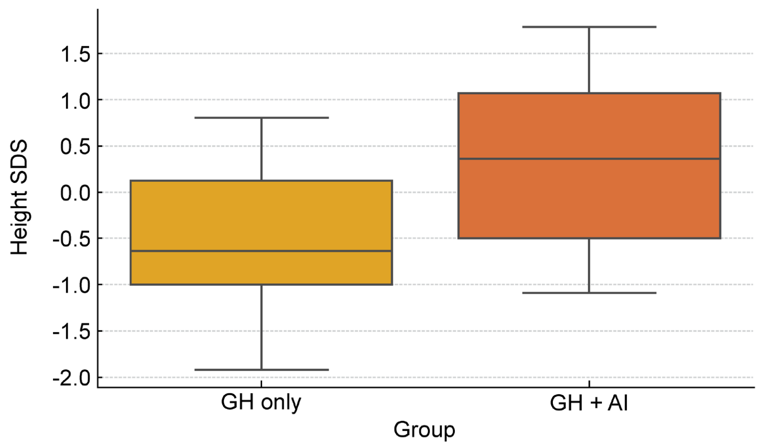

Figure 2. Change in height SDS before and after treatment in the GH-only and GH + AI groups. The GH + AI group demonstrates a significant improvement (p = 0.048), despite limited growth potential due to older age and bone maturity. GH, growth hormone; AI, aromatase inhibitor; SDS, standard deviation score.

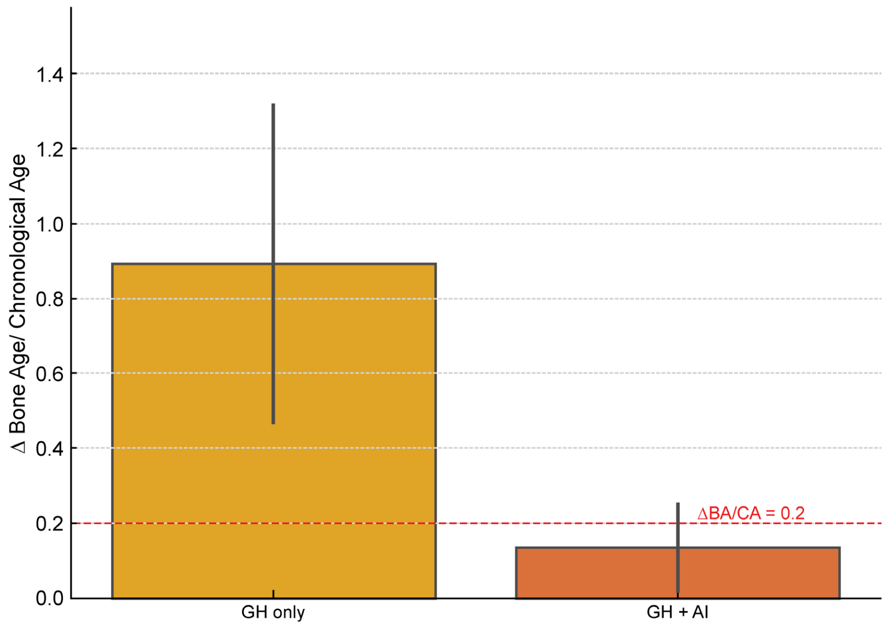

Figure 3. ΔBA/CA ratio in the GH-only and GH + AI groups. Each dot represents an individual participant's ΔBA/CA ratio. Bars indicate mean ± SD. The GH + AI group exhibits a significantly lower mean ΔBA/CA ratio than the GH-only group (p = 0.046), suggesting effective suppression of bone maturation. A red dashed line at ΔBA/CA = 0.2 indicates the clinical threshold, with 74.1% of patients in the GH + AI group falling below this value. GH, growth hormone; AI, aromatase inhibitor; ΔBA/CA, change in bone age/chronological age; SD, standard deviation.

To further explore the clinical importance of bone age suppression, individual response analysis showed that 20 out of 27 patients (74.1%) in the GH + AI group exhibited a ΔBA/CA ratio below 0.2. Although the GH + AI group showed a numerically higher frequency of acne than the GH-only group (44.4% vs. 25.0%), no serious dermatologic or systemic adverse events were observed, and all patients completed the treatment protocol.

Table 3. Adverse events.

Adverse Event	GH-only	GH + AI	p-value
Arthralgia	0 (0.0%)	1 (3.7%)	1.000
Edema	0 (0.0%)	0 (0.0%)	1.000
Hair loss	0 (0.0%)	2 (7.4%)	1.000
Acne	2 (25.0%)	12 (44.4%)	0.431
Hematologic adverse event	0 (0.0%)	0 (0.0%)	1.000

GH, growth hormone; AI, aromatase inhibitor.

4. Discussion

This study demonstrated that the combination of AI and GH therapy was effective and well tolerated without major adverse effects in Korean boys with ISS and advanced bone age. Although the annual growth velocity in the GH + AI group was lower than that in the GH-only group, the observed growth was clinically meaningful, as reflected by a greater improvement in height SDS and a significant reduction in bone age progression (ΔBA/CA). These findings support the hypothesis that AIs can delay epiphyseal fusion and extend the growth period in boys during late puberty [21]-[24]. These findings may serve as practical evidence for clinicians making treatment decisions in this specific population.

GnRH analog (GnRHa) and GH combination therapy has also been reported to be effective in increasing height in some studies, but the results were inconsistent [25]-[28]. In particular, GnRHa treatment effectively delays bone fusion but can cause a state of decreased gonad function at an important time of puberty, which may negatively affect physical and psychosocial development [29] [30].

The key mechanism underlying the effect of AIs is the suppression of estrogen biosynthesis. Estrogen is the primary regulator of epiphyseal closure in both sexes, as evidenced by males with aromatase deficiency or estrogen receptor mutations who demonstrate continued linear growth and delayed skeletal maturation despite normal or elevated androgen levels [10] [11]. By inhibiting aromatase activity, AIs block the conversion of androgens to estrogens, reducing estrogen-mediated chondrocyte senescence and apoptosis at the growth plate [8] [16]. This mechanism allows for continued proliferation and hypertrophy of chondrocytes, prolonging linear growth during late puberty when the window for height gain is limited [3].

Previous studies support the use of AIs in boys with ISS. Hero *et al.* reported that letrozole administration in adolescent boys with ISS delayed bone maturation and increased predicted adult height by 5.9 cm over 2 years [16]. Similarly, Mauras *et al.* reported that 24 - 36 months of combined AI and GH therapy resulted in greater height gains than either treatment alone, with the AI + GH group showing an absolute increase of 22.5 cm compared with 20.6 cm in the GH group and 18.2

cm in the AI group [17]. Anastrozole use over 3 years in GH-treated boys also demonstrated sustained improvements in predicted adult height in a multicenter placebo-controlled trial [14]. Beyond ISS, clinical studies have shown that letrozole monotherapy in boys with constitutional delay of puberty significantly increases predicted or near-final adult height, supporting broader applicability of AIs in pubertal growth modulation [31].

Despite these positive results, there are still concerns about long-term safety and off-label use in children. AIs are not officially licensed drugs for height growth purposes, and there is a high legal and ethical burden [32]. Domestic academia, including the Korean Society of Pediatric Endocrionology, is taking a cautious approach to AI use. While clinical studies have not established long-term reproductive risks, theoretical concerns based on hormonal modulation suggest the need for close follow-up, particularly in pubertal patients. Furthermore, prescribing off-label drugs represents a substantial burden for physicians [33]. However, in late pubertal boys with advanced bone age, GH alone is often ineffective, making AI + GH combination therapy the only viable option for achieving meaningful height gains. Families in this study strongly desired such therapy, recognizing that being below average height imposes not only cosmetic concerns but also profound emotional and social impacts. To protect patients and physicians, broader discussions and the development of policies supporting the safe and effective use of off-label therapies are urgently needed.

In this study, the annual growth rate in the GH + AI group was lower than that in the GH-only group, but this is attributable to the advanced bone age and limited growth capacity at baseline in the combined group. Nevertheless, the reduced ΔBA/CA in the GH + AI group suggests a potential for greater cumulative height gain over time if treatment is continued. Elevated IGF-1 and IGFBP-3 levels observed at the end of therapy further indicate that GH dosing was effectively titrated to support growth in these patients. Although the differences in IGF-1 and IGFBP-3 levels between groups may reflect relatively higher GH exposure in older, more skeletally mature patients, aromatase inhibition itself can also elevate IGF-1 levels by reducing estrogen-mediated suppression of hepatic IGF-1 synthesis. Thus, the observed increase in IGF-1 is likely due to a combination of both factors rather than GH dosing alone. However, elevated IGF-1 levels should be interpreted cautiously given their potential association with adverse outcomes.

This study has some limitations. The retrospective design and small sample size limit the generalizability of our findings. Additionally, the short treatment duration precludes assessment of final adult height. While prior prospective studies suggest potential benefits on predicted adult height, long-term data on actual attained height remain scarce.

5. Conclusion

This study suggests that combined treatment with growth hormone and an aromatase inhibitor can slow bone maturation and support linear growth in Korean boys with idiopathic short stature and advanced bone age. Such therapy may be considered in late-pubertal patients with limited growth potential, where growth hormone alone is often insufficient. Because aromatase inhibitors are used off-label and long-term safety data are lacking, treatment should be restricted to carefully selected patients and undertaken with close monitoring of pubertal progression, bone health, and metabolic status. Ethical and legal concerns may also limit clinical application, highlighting the need for clearer guidance and supportive policy. Larger prospective studies are required to confirm these findings and to assess final adult height and long-term safety.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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