Observational Study

Medicine®

OPEN

Factors affecting bone age maturation during 3 years of growth hormone treatment in patients with idiopathic growth hormone deficiency and idiopathic short stature

Analysis of data from the LG growth study

Min Jae Kang, MD, PhD[a], Eun Young Kim, MS[b], Young Suk Shim, MD, MS[a], Hwal Rim Jeong, MD, PhD[a], Hye Jin Lee, MD, MS[a], Seung Yang, MD, PhD[a], Il Tae Hwang, MD, PhD[a,*]

Abstract

To investigate the progression rate of bone age (BA) and associated factors during the first 3 years of growth hormone (GH) treatment in children with idiopathic GH deficiency (iGHD) and idiopathic short stature (ISS).

Data for prepubertal children with iGHD and ISS who were treated with recombinant human GH were obtained from the LG Growth Study Database and analyzed. Height, weight, BA, insulin-like growth factor-1 (IGF-1) level, and GH dose were recorded every 6 months. Differences between BA and chronological age (CA), BA-CA, were calculated at each measurement. This study included 92 (78 iGHD and 14 ISS) subjects.

After 3 years of GH treatment, the height *z*-score was -1.09 ± 0.71 ($P < .001$ compared to baseline), BA-CA was -1.21 ± 1.18 years ($P < .001$), and IGF-1 standard deviation score (SDS) was 0.43 ± 1.21 ($P < .001$) in the iGHD subjects; the change in BA over the 3 years was 3.68 ± 1.27 years. In the ISS subjects, the height *z*-score was -1.06 ± 0.59 ($P < .001$), BA-CA was -0.98 ± 1.23 years ($P = .009$), and IGF-1 SDS was 0.16 ± 0.76 ($P = .648$); the change in BA over the 3 years was 3.88 ± 1.36 years. The only significant factor associated with the BA progression was the BA-CA at 1 year of GH treatment (OR = 2.732, $P = .001$). The baseline BA-CA, IGF-1 SDS, and GH dose did not influence BA progression.

Prepubertal subjects with iGHD and ISS showed height improvement and mild BA acceleration over the first 3 years of GH treatment. However, because the BA progression rate was considered to be clinically acceptable, GH treatment may increase the predicted adult height during this period.

Abbreviations: BA = bone age, BMI = body mass index, CA = chronological age, GH = growth hormone, GHD = GH deficiency, IGF-1 = insulin-like growth factor-1, IGFBP-3 = IGF-binding protein-3, iGHD = idiopathic GHD, ISS = idiopathic short stature, LGS = LG Growth Study, MMRM = mixed-effects model repeated measures, SD = standard deviation, SDS = standard deviation score.

Keywords: bone age, growth hormone, growth hormone deficiency, idiopathic short stature

1. Introduction

Many signals are involved in growth plate maturation, including growth hormone (GH), insulin-like growth factor-1 (IGF-1), glucocorticoids, thyroid hormone, estrogen, androgen, vitamin D, leptin, paracrine factors, extracellular matrix, and intracellular mechanisms.[1–3] GH and IGF-1 are traditionally considered potent stimulators of bone growth.[1] In children with GH deficiency (GHD), bone age (BA) is significantly delayed compared to chronological age (CA). After GH treatment, increased serum IGF-1 or GH levels stimulate growth plate development and result in BA progression. Usually, BA progression rates within 1 year of CA are considered normal, but some studies have found that various rates of skeletal maturation can be associated with underlying diseases,[4,5] pubertal status, and obesity.[6] BA changes can be erratic over time, even in normal healthy boys.[7,8]

The goal of GH treatment is to increase final adult height. When predicting adult height, the Bayley and Pinneau method use specific tables for delayed, average, and advanced BA which are determined by the Greulich and Pyle hand standards.[9] Therefore, the BA progression rate during GH treatment has an important impact on adult height prediction. Nonetheless, the BA progression rate of those who receive GH treatment varies and can be either within the normal range[10–12] or accelerated,[7,13–15] and the results may be affected by age, sex, underlying disease, GH dose, duration of GH treatment, or pubertal status.

Editor: Eva Feigerlova.

Disclosure of potential conflicts of interest: ITH is a member of the Observational Study Monitoring Board of the LG Growth Study. EYK is a full-time employee of LG Chem, Ltd.

ORCID: 0000-0002-3885-4322

[a] Department of Pediatrics, Hallym University College of Medicine, Chuncheon-si, Gangwon-do, [b] Life Science R&D, LG Chem, Ltd., Gangseo-gu, Seoul, Republic of Korea.

[*] Correspondence: Il Tae Hwang, Department of Pediatrics, Kangdong Sacred Heart Hospital, 150, Seongan-ro, Gangdong-gu, Seoul 05355, Republic of Korea (e-mail: ithwang83@hallym.or.kr).

Medicine (2019) 98:14(e14962)

Received: 25 June 2018 / Received in final form: 28 February 2019 / Accepted: 2 March 2019

http://dx.doi.org/10.1097/MD.0000000000014962

As the height at onset of puberty and final height are closely associated, maximizing the duration of prepubertal GH treatment may be beneficial.[16] However, data on the BA progression rate of prepubertal patients with GHD over long-term GH treatment are insufficient. Therefore, we investigated the progression rate of BA during the first 3 years of GH treatment in prepubertal children with idiopathic GHD (iGHD) and idiopathic short stature (ISS) based on data obtained from the LG Growth Study (LGS). We also analyzed factors associated with the rapid progression of BA in children with iGHD.

2. Materials and methods

Data of prepubertal children with iGHD and ISS who were treated with recombinant human GH (Eutropin inj., EutropinAQ inj., and EutropinPlus inj., LG Chem, Ltd, Korea) were obtained from the LGS Database and assessed in our study. The LGS has been in progress since 2012 and is an open-label, multicenter, prospective, and retrospective observational study.[17] Informed consent was obtained from all participants before the study enrollment period. The institutional review board of Hallym University Sacred Heart Hospital approved this study (IRB# 2017-I129).

Idiopathic GHD was defined when all of the following criteria were met: (1) height below the third percentile; (2) peak GH levels below 10 μg/L in two standard stimulation tests; and (3) BA delayed compared to CA.

Idiopathic short stature was defined when a child with normal birth weight and height was below the third percentile of height, had normal GH responses in stimulation tests and no chromosomal abnormality, and lacked any other identifiable disease related to short stature. The participants were treated with GH for at least 3 years, and the height, weight, body mass index (BMI), pubertal status, BA, IGF-1, and IGF-binding protein-3 (IGFBP-3) values were recorded at baseline and during follow-up. The GH dose was individualized after the recommended initial dose. The posology was then adapted at the first-, second-, and third-year follow-up evaluations. Only subjects in the prepubertal stage at baseline and during the follow-up period were included. BA was determined by the treating physician and was based on the standards of Greulich and Pyle.[18] Differences between BA and CA were calculated at each measurement and defined as follows: BA0-CA0, at baseline; BA1-CA1, at the end of the first year of GH treatment; BA2-CA2, at the end of the second year of GH treatment; BA3-CA3, at the end of the third year of GH treatment. All anthropometric measurements were converted to *z*-scores using a Korean growth standard.[19] The IGF-1 standard deviation score (SDS) and IGFBP-3 SDS values were calculated using the Korean normal reference.[20] Subjects with at least 1 missing anthropometric or BA measurement during the 3-year follow-up period were excluded. Finally, 92 (78 iGHD and 14 ISS) subjects were included in this study.

2.1. Statistical analysis

All data are presented as the mean ± standard deviation (SD). Differences in anthropometric measurements and BA between the iGHD and ISS subjects were compared using Student *t* test or Wilcoxon rank sum test. Differences in the BA-CA values during GH treatment, compared to their basal values, were investigated by paired *t* tests. Serial changes of anthropometric measurements and BA were analyzed using a mixed-effects model repeated measures (MMRM) approach. Comparisons of BA progression according to baseline BA characteristics were analyzed using McNemar test. A comparison of factors associated with the rapid progression of BA at 3 years of GH treatment (BA3-CA3 ≥ −1.00 year) was performed using multiple logistic regression analysis. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC). *P*-values of <.05 were considered significant.

Table 1

Clinical characteristics of subjects during GH treatment.

	iGHD (n = 78)	ISS (n = 14)
Baseline (before GH treatment)		
CA, yr	7.80 ± 2.77	8.14 ± 2.97
Height *z*-score	−2.45 ± 0.67	−2.60 ± 0.62
BMI *z*-score	−0.24 ± 1.08	−0.28 ± 0.93
BA-CA, yr	−1.99 ± 0.96	−2.04 ± 1.25
1 year of GH treatment		
CA, yr	8.91 ± 2.78	9.10 ± 2.99
Height *z*-score	−1.75 ± 0.69	−1.77 ± 0.66
BMI *z*-score	−0.30 ± 0.93	−0.31 ± 0.97
BA-CA, yr	−1.80 ± 1.03	−1.67 ± 1.70
BA (1 yr)-BA (baseline)	1.21 ± 0.82	1.39 ± 0.84
GH dose, mg/kg/wk	0.33 ± 0.16	0.30 ± 0.14
2 yr of GH treatment		
CA, yr	9.91 ± 2.77	9.96 ± 2.91
Height *z*-score	−1.35 ± 0.67	−1.40 ± 0.58
BMI *z*-score	−0.31 ± 1.00	−0.48 ± 0.83
BA-CA, yr	−1.43 ± 0.97	−1.23 ± 1.48
BA (2 yr)-BA (1 yr)	1.35 ± 0.86	1.42 ± 0.72
BA (2 yr)-BA (baseline)	2.56 ± 0.94	2.81 ± 0.94
GH dose, mg/kg/wk	0.28 ± 0.14	0.25 ± 0.11
3 yr of GH treatment		
CA, yr	10.8 ± 2.75	11.71 ± 3.83
Height *z*-score	−1.09 ± 0.71	−1.06 ± 0.59
BMI *z*-score	−0.22 ± 1.15	−0.58 ± 0.82
BA-CA, yr	−1.21 ± 1.18	−0.98 ± 1.23
BA (3 yr)-BA (2 yr)	1.12 ± 0.75	1.06 ± 1.00
BA (3 yr)-BA (baseline)	3.68 ± 1.27	3.88 ± 1.36
GH dose, mg/kg/wk	0.25 ± 0.12	0.22 ± 0.09

Data are expressed as mean ± SD.

BA = bone age, BMI = body mass index, CA = chronological age, GH = growth hormone, iGHD = idiopathic growth hormone deficiency, ISS = idiopathic short stature.

3. Results

3.1. Clinical characteristics of subjects (Table 1)

Of the 78 subjects (47 boys, 31 girls) with iGHD, the mean age at baseline (before GH treatment) was 7.80 ± 2.77 years. The height and BMI *z*-scores were −2.45 ± 0.67 and −0.24 ± 1.08, respectively. Their BA was 1.99 ± 0.96 years delayed compared to their CA. The IGF-1 SDS and IGFBP-3 SDS values were −0.89 ± 0.90 and −0.29 ± 1.76, respectively. After 3 years of GH treatment, the height *z*-score was −1.09 ± 0.71, which was significantly different from to the baseline height ($P < .001$), BA3-CA3 was −1.21 ± 1.18 years ($P < .001$ compared to BA0-CA0), and the BA change over the 3 years was 3.68 ± 1.27 years. The IGF-1 SDS and IGFBP-3 SDS values were 0.43 ± 1.21 ($P < .001$ compared to baseline IGF-1 SDS) and 0.67 ± 2.09 ($P = .034$ compared to baseline IGFBP-3 SDS), respectively, with a GH dose of 0.25 ± 0.12 mg/kg/wk. There were no differences between males and females in the clinical characteristics at baseline or during follow-

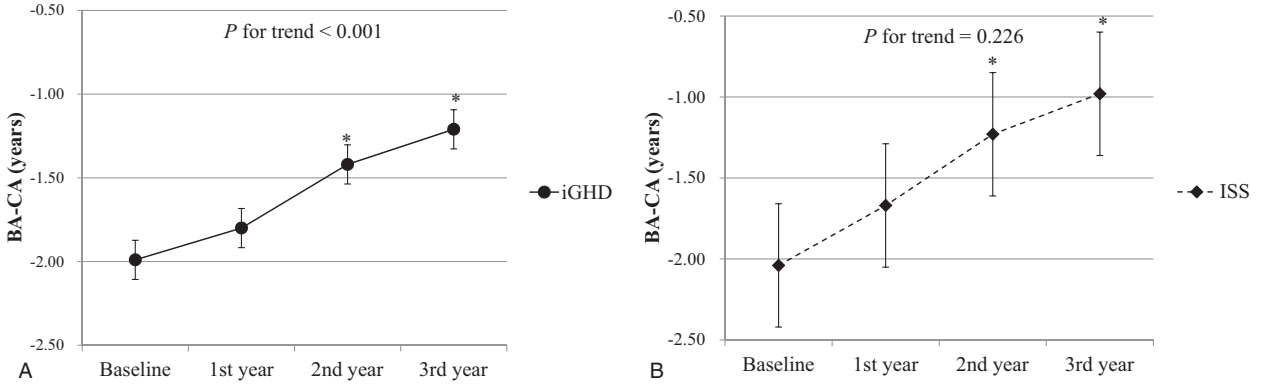

Figure 1. BA-CA changes during GH treatment in subjects with iGHD (A) and ISS (B) are shown. $^{*}P < .05$ compared to baseline BA-CA by the MMRM approach. BA = bone age, CA = chronological age, GH = growth hormone, iGHD = idiopathic GHD, ISS = idiopathic short stature, MMRM = mixed-effect model repeated measure.

up, except for BA3-CA3 (males; -1.57 ± 1.16 vs females; -0.66 ± 1.00; $P = .001$).

Of the 14 subjects (8 boys, 6 girls) with ISS, the mean age at baseline was 8.14 ± 2.97 years. The height and BMI *z*-scores were -2.60 ± 0.62 and -0.28 ± 0.93, respectively. Their BA was 2.04 ± 1.25 years delayed compared to their CA. Their IGF-1 SDS and IGFBP-3 SDS values were -0.31 ± 0.78 and -0.93 ± 0.88, respectively. After 3 years of GH treatment, the height *z*-score was -1.06 ± 0.59 ($P < .001$ compared to baseline height *z*-score). BA3-CA3 was -0.98 ± 1.23 years ($P = .009$ compared to BA0-CA0), and the BA change over the 3 years was 3.88 ± 1.36 years. The IGF-1 SDS and IGFBP-3 SDS values were 0.16 ± 0.76 ($P = .648$ compared to baseline IGF-1 SDS) and -0.62 ± 0.24 ($P = .881$ compared to baseline IGFBP-3 SDS), respectively, with a GH dose of 0.22 ± 0.09 mg/kg/wk.

The baseline characteristics of height, BMI, and BA-CA showed no significant differences between the iGHD and ISS cohorts. Height *z*-score, BMI *z*-score, BA, IGF-1 SDS, and IGFBP-3 SDS changes during the 3 years of GH treatment did not differ between the iGHD and ISS cohorts.

3.2. BA-CA and IGF-1 SDS changes during the 3 years of GH treatment (Figs. 1 and 2)

In subjects with iGHD, mean BA-CA values were -1.80 ± 1.03 years at the end of 1 year of GH treatment ($P = .074$ compared to BA0-CA0), -1.43 ± 0.97 years at the end of 2 years ($P < .001$ compared to BA0-CA0), and -1.21 ± 1.18 years at the end of 3 years ($P < .001$ compared to BA0-CA0). BA-CA changes were significant in the second year of GH treatment (P for trend = .024 by the MMRM approach, Fig. 2A). Changes in BA during the 1-year intervals were 1.21 ± 0.82 years (in the first year of GH treatment), 1.35 ± 0.86 years (in the second year of GH treatment), and 1.12 ± 0.75 years (in the third year of GH treatment). The IGF-1 SDS increased prominently during the first year of GH treatment ($P < .001$ compared to baseline IGF-1 SDS), but no significant changes were found thereafter (Fig. 2A).

In subjects with ISS, mean BA-CA values were -1.67 ± 1.70 years at the end of 1 year of GH treatment ($P = .129$ compared to BA0-CA0), -1.23 ± 1.48 years at the end of 2 years ($P = .007$ compared to BA0-CA0), and -0.98 ± 1.23 years at the end of 3 years ($P = .009$ compared to BA0-CA0). BA-CA changes did not show significant differences during the 3 years of GH treatment (Fig. 2B). Changes in BA in 1-year intervals were 1.39 ± 0.84 years (in the first year of GH treatment), 1.42 ± 0.72 years (in the second year of GH treatment), and 1.06 ± 1.00 years (in the third year of GH treatment). The IGF-1 SDS increased prominently during the first year of GH treatment ($P = .003$ compared to baseline IGF-1 SDS), but the IGF-1 SDS then exhibited a decreasing trend (Fig. 2B).

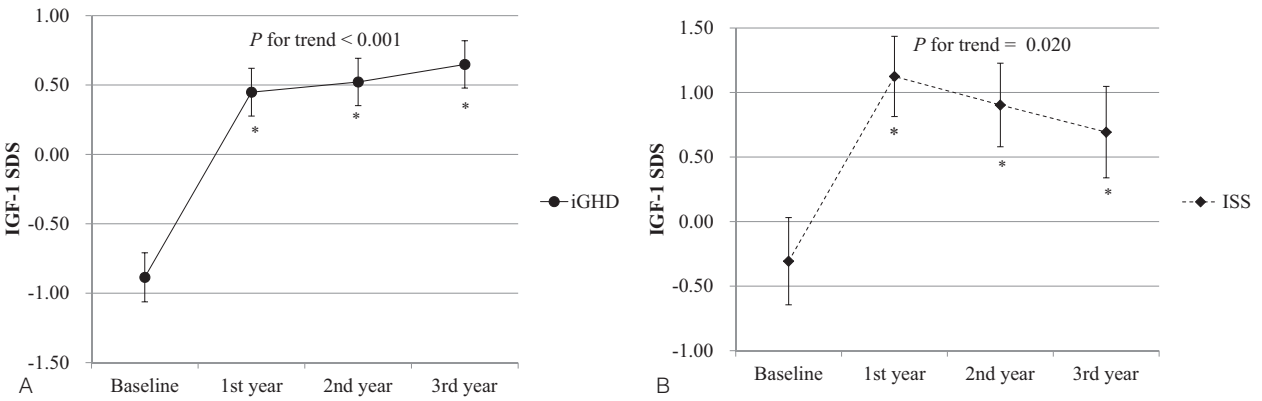

Figure 2. IGF-1 SDS changes during GH treatment in subjects with iGHD (A) and ISS (B) are shown. $^{*}P < .05$ compared to baseline IGF-1 SDS by the MMRM approach. GH = growth hormone, IGF-1 = insulin-like growth factor-1, iGHD = idiopathic GHD, ISS = idiopathic short stature, MMRM = mixed-effect model repeated measure, SDS = standard deviation score.

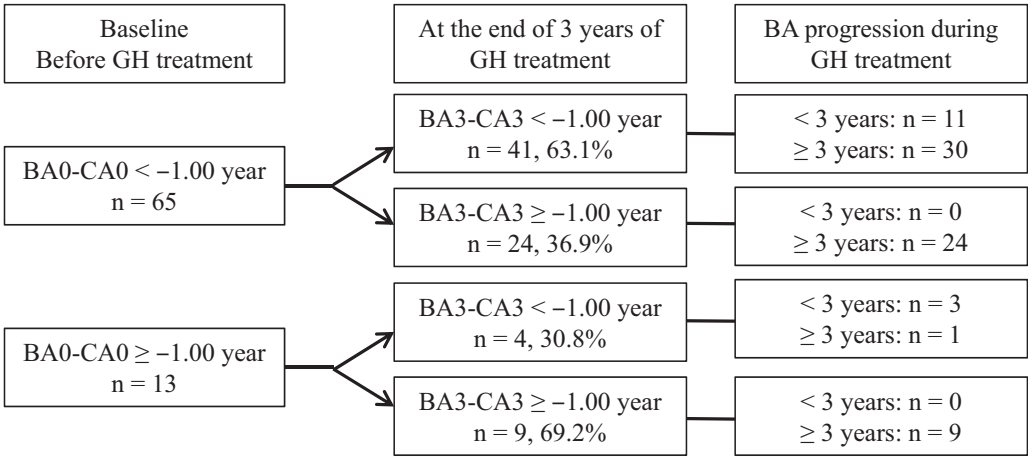

Figure 3. Progression of bone age during GH treatment according to baseline characteristics in subjects with iGHD. GH = growth hormone, iGHD = idiopathic GHD.

3.3. Factors associated with BA progression during GH treatment in iGHD subjects

BA progression greater than 3 years during GH treatment was found in 82.1% (64/78) of the subjects with iGHD. The BA progressions showed significant differences according to delayed BA baseline status ($P < .001$, Fig. 3). Of the 65 subjects who showed a BA0-CA0 < -1.00 year, 63.1% had a BA3-CA3 < -1.00 year, while 69.2% of the 13 subjects who showed a BA0-CA0 ≥ -1.00 year had a BA3-CA3 ≥ -1.00 year. However, the only significant factor associated with BA3-CA3 was BA1-CA1 (OR = 2.732; 95% CI, 1.495–4.993; $P = .001$, Fig. 4), after adjusting for other variables, including sex, age, and baseline BA delay. BA0-CA0 showed positive relationships with BA3-CA3 in a simple correlation analysis ($r = 0.333$, $P = .003$), but these correlations were not significant in the multiple logistic regression analysis. The IGF-SDS and IGFBP-3 SDS at the end of the third year of GH treatment and the GH dose did not influence BA3-CA3.

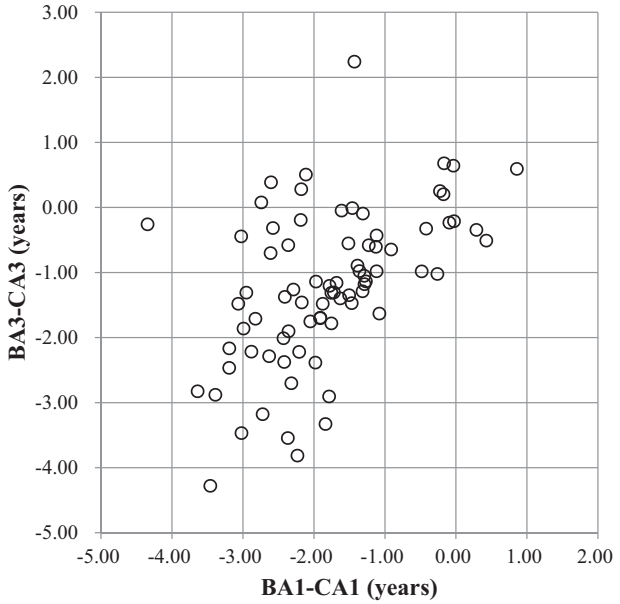

Figure 4. BA1-CA1 was significantly positively associated with BA3-CA3 (OR = 2.732; 95% CI: 1.495–4.993; $P = .001$). BA1-CA1 = difference between BA and CA at the end of the first year of GH treatment, BA3-CA3 = difference between BA and CA at the end of the third year of GH treatment. BA = bone age, CA = chronological age, CI = confidence interval, GH = growth hormone, OR = odds ratio.

4. Discussion

In summary, 3 years of GH treatment resulted in significant height improvements in both iGHD and ISS cohorts, as based on height *z*-scores. The progression of BA (iGHD, 3.68 years; ISS 3.88 years) was slightly greater than that of CA during the 3 years of GH treatment; however, the mean values were considered clinically acceptable. The BA progression/year of CA was not accelerated over the treatment period (iGHD, 1.12 years and ISS, 1.06 years at the third year of GH treatment). Finally, the progression of BA after the first year of GH treatment affected BA maturation over the 3 years of GH treatment in subjects with iGHD, and contrary to our expectations, IGF-1 SDS changes were not relevant to BA progression.

The progression rate of BA during GH treatment in subjects with iGHD has been reported in previous studies to vary between 0.7 and 1.6 years/year of CA.[12,21–25] Darendeliler *et al.* suggested that a BA progression of less than 2 yr/yr of CA can be considered normal, at least during the prepubertal period,[4] and Benso et al found that BA progression varied from 0.5 yr/yr to over 2 yr/yr in normal boys.[8] A study with similar conditions to ours (prepubertal at the start of GH treatment, a GH dose of 0.35 mg/kg/wk and 2 years of GH treatment) by Cohen et al reported 1.2 years of BA progression/year of CA,[24] which was consistent with our findings (1.28 years of BA progression/year of CA). Many confounding factors may impact these diverse results, but among them, pubertal status is an important factor. Prolonged exposure to elevated levels of estradiol or testosterone is needed to markedly accelerate BA maturation during puberty.[26] Kawai et al[13] and Hopwood et al[14] studied the efficacy of GH treatment in terms of improving final adult height in non-GHD or GHD subjects presenting with short stature and found 2 opposite results according to pubertal status; treatment was beneficial when the subject remained prepubertal versus not beneficial when the subject became pubertal during treatment. To

control this important confounding factor, we only included prepubertal subjects. Our findings suggest that 3 years of GH treatment at a conventional dose in prepubertal subjects with iGHD did not adversely affect BA maturation.

ISS is a growth disorder that is associated with normal stimulation of GH secretion, and the degree of BA delay and the recommended initial GH dose for patients with ISS differ from those of iGHD.[25] However, in our study, baseline clinical characteristics, including GH dose and IGF-1 SDS, showed no differences between the iGHD and ISS groups. This could lead to similar BA progression patterns in subjects with ISS and those with iGHD, and this observation has also been found in other studies.[4,27]

Regarding factors affecting BA maturation, previous studies have indicated that baseline BA delay is positively correlated with BA progression.[4,12] Our study identified similar correlation patterns between the progression rate of BA and baseline BA delay; however, when other factors were considered, the statistical significance was marginal. Interestingly, BA delay at the end of the first year of GH treatment was found to be a significant factor that predicted BA delay at the end of the third year of GH treatment in our study. This result may be associated with IGF-1 SDS changes. Independent of sex or pubertal stage, IGF-1 plays a well-known role in skeletal maturation.[28] In previous studies, increased IGF-1 levels due to GH treatment were found to be the main factor for growth response,[29] and BA/CA groups, according to tertiles, showed positive correlations with IGF-1 *z*-scores among subjects who received GH treatment.[6] In our study, IGF-1 SDS changes displayed a sharp increase during the first year of GH treatment, which could have significantly affected the BA1-CA1. However, the IGF-1 SDS did not increase after the first year, while height *z*-scores consistently improved over time during GH treatment, in both the iGHD and ISS cohorts. We did not identify a direct correlation between the IGF-1 SDS and BA progression; however, these findings emphasize the meaning of BA1-CA1 in this study.

There is an unavoidable difficulty in the method of BA estimation used in this study. Because this was a multicenter study, inter-observer differences occurred when determining BA. We used the interpretation of BA based on the Greulich and Pyle hand atlas, which could be subjective. However, when considering the prediction of adult height, the Greulich and Pyle method are suggested to be more accurate than other BA assessment methods such as the Tanner-Whitehouse 2 method.[30] Additionally, the LGS data were valuable because they originated from a multicenter database, which could attenuate investigator bias.

In conclusion, both the iGHD and ISS prepubertal cohorts showed height improvement and mild BA acceleration over the first 3 years of GH treatment. However, because the BA progression rate is considered clinically acceptable, GH treatment may increase the predicted adult height during this period.

Acknowledgments

We thank all of the physicians who contributed their patient data to the LG Growth Study.

Author contributions

Conceptualization: Min Jae Kang, Il Tae Hwang.
Data curation: Min Jae Kang, Eun Young Kim.
Formal analysis: Min Jae Kang, Eun Young Kim.
Methodology: Min Jae Kang, Eun Young Kim.
Project administration: Min Jae Kang.
Resources: Eun Young Kim.
Software: Eun Young Kim.
Supervision: Seung Yang, Il Tae Hwang.
Validation: Young Suk Shim, Hwal Rim Jeong, Hye Jin Lee, Seung Yang.
Visualization: Young Suk Shim, Hwal Rim Jeong, Hye Jin Lee, Seung Yang.
Writing – original draft: Min Jae Kang.
Writing – review and editing: Min Jae Kang, Il Tae Hwang.
Min Jae Kang orcid: 0000-0003-3080-0941.
Il Tae Hwang orcid: 0000-0002-3885-4322.

References

[1] Nilsson O, Marino R, De Luca F, et al. Endocrine regulation of the growth plate. Horm Res 2005;64:157–65.
[2] Baron J, Savendahl L, De Luca F, et al. Short and tall stature: a new paradigm emerges. Nat Rev Endocrinol 2015;11:735–46.
[3] Fimmel S, Saborowski A, Terouanne B, et al. Inhibition of the androgen receptor by antisense oligonucleotides regulates the biological activity of androgens in SZ95 sebocytes. Horm Metab Res 2007;39:149–56.
[4] Darendeliler F, Ranke MB, Bakker B, et al. Bone age progression during the first year of growth hormone therapy in pre-pubertal children with idiopathic growth hormone deficiency, Turner syndrome or idiopathic short stature, and in short children born small for gestational age: analysis of data from KIGS (Pfizer International Growth Database). Horm Res 2005;63:40–7.
[5] Haeusler G, Schemper M, Frisch H, et al. Spontaneous growth in Turner syndrome: evidence for a minor pubertal growth spurt. Eur J Pediatr 1992;151:283–7.
[6] Klein KO, Newfield RS, Hassink SG. Bone maturation along the spectrum from normal weight to obesity: a complex interplay of sex, growth factors and weight gain. J Pediatr Endocrinol Metab 2016;29:311–8.
[7] Wilson DM. Regular monitoring of bone age is not useful in children treated with growth hormone. Pediatrics 1999;104:1036–9.
[8] Benso L, Vannelli S, Pastorin L, et al. Variation of bone age progression in healthy children. Acta Paediatr Suppl 1997;423:109–12.
[9] Bayley N, Pinneau SR. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. J Pediatr 1952;40:423–41.
[10] Lesage C, Walker J, Landier F, et al. Near normalization of adolescent height with growth hormone therapy in very short children without growth hormone deficiency. J Pediatr 1991;119:29–34.
[11] Zadik Z, Chalew S, Zung A, et al. Effect of long-term growth hormone therapy on bone age and pubertal maturation in boys with and without classic growth hormone deficiency. J Pediatr 1994;125:189–95.
[12] Frindik JP, Kemp SF, Sy JP. Effects of recombinant human growth hormone on height and skeletal maturation in growth hormone-deficient children with and without severe pretreatment bone age delay. Horm Res 1999;51:15–9.
[13] Kawai M, Momoi T, Yorifuji T, et al. Unfavorable effects of growth hormone therapy on the final height of boys with short stature not caused by growth hormone deficiency. J Pediatr 1997;130:205–9.
[14] Hopwood NJ, Hintz RL, Gertner JM, et al. Growth response of children with non-growth-hormone deficiency and marked short stature during three years of growth hormone therapy. J Pediatr 1993;123:215–22.
[15] Wit JM, Fokker MH, de Muinck Keizer-Schrama SM, et al. Dutch Growth Hormone Working GroupEffects of two years of methionyl growth hormone therapy in two dosage regimens in prepubertal children with short stature, subnormal growth rate, and normal growth hormone response to secretagogues. J Pediatr 1989;115:720–5.
[16] Kamp GA, Waelkens JJ, de Muinck Keizer-Schrama SM, et al. High dose growth hormone treatment induces acceleration of skeletal maturation and an earlier onset of puberty in children with idiopathic short stature. Arch Dis Child 2002;87:215–20.
[17] Chung S, Yoo JH, Choi JH, et al. Design of the long-term observational cohort study with recombinant human growth hormone in Korean children: LG Growth Study. Ann Pediatr Endocrinol Metab 2018;23:43–50.
[18] Greulich WW, Pyle SI. Radiographic Atlas of Skeletal Development of the Hand and Wrist. Stanford, CA: Standford University Press; 1959.
[19] Korean Children and Adolescents Growth Standard [Internet]. 2007 [cited January 2018]. Available at: http://www.cdc.go.kr/webcdc. Accessed January 2018

[20] Hyun SE, Lee BC, Suh BK, et al. Reference values for serum levels of insulin-like growth factor-I and insulin-like growth factor binding protein-3 in Korean children and adolescents. Clin Biochem 2012;45: 16–21.
[21] Hochberg Z, Leiberman E, Landau H, et al. Age as a determinant of the impact of growth hormone therapy on predicted adult height. Clin Endocrinol (Oxf) 1994;41:331–5.
[22] Birnbacher R, Riedl S, Frisch H. Long-term treatment in children with hypopituitarism: pubertal development and final height. Horm Res 1998;49:80–5.
[23] Severi F. Final height in children with growth hormone deficiency. Horm Res 1995;43:138–40.
[24] Cohen P, Bright GM, Rogol AD, et al. Effects of dose and gender on the growth and growth factor response to GH in GH-deficient children: implications for efficacy and safety. J Clin Endocrinol Metab 2002;87:90–8.
[25] Mauras N, Attie KM, Reiter EO, et al. Genentech, Inc., Cooperative Study GroupHigh dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. J Clin Endocrinol Metab 2000;85:3653–60.
[26] Lazar L, Lebenthal Y, Shalitin S, et al. Natural history of idiopathic advanced bone age diagnosed in childhood: pattern of growth and puberty. Horm Res Paediatr 2011;75:49–55.
[27] Im M, Kim YD, Han HS. Effect of growth hormone treatment on children with idiopathic short stature and idiopathic growth hormone deficiency. Ann Pediatr Endocrinol Metab 2017;22:119–24.
[28] Reinehr T, de Sousa G, Wabitsch M. Relationships of IGF-I and andrrogens to skeletal maturation in obese children and adolescents. J Pediatr Endocrinol Metab 2006;19:1133–40.
[29] Kristrom B, Lundberg E, Jonsson B, et al. IGF-1 and growth response to adult height in a randomized GH treatment trial in short non-GH-deficient children. J Clin Endocrinol Metab 2014;99:2917–24.
[30] Zachmann M, Sobradillo B, Frank M, et al. Bayley-Pinneau, Roche-Wainer-Thissen, and Tanner height predictions in normal children and in patients with various pathologic conditions. J Pediatr 1978;93:749–55.