Eungu Kang, Lindsey Yoojin Chung, Young-Jun Rhie, Kee-Hyoung Lee and Hyo-Kyoung Nam*

Long-term effectiveness and safety of long-acting growth hormone preparation in children with growth hormone deficiency

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Abstract

Objectives: To evaluate the long-term effectiveness of weekly vs. daily growth hormone (GH) administration in children with GH deficiency.

Methods: This study, part of the "LG Growth Study", included a total of 996 children with GH deficiency (773 receiving daily GH and 193 receiving weekly GH). Anthropometric data were collected at baseline and every 12 months; clinical and laboratory data were collected at baseline and throughout the study.

Results: At baseline, the weekly GH group was older, shorter in mid-parental height (MPH), and had more pubertal boys compared to the daily GH group (age: 8.46 ± 3.44 vs. 7.46 ± 2.89 years, p<0.001; MPH: −0.88 ± 0.73 SD vs. −1.02 ± 0.84 SD, p=0.044; pubertal boys: 34.0 vs. 16.9 %, p=0.006). Height velocity and change in height SDS during the first 12 months were higher in the daily GH group (height velocity: 9.06 ± 1.72 vs. 8.67 ± 1.98 cm/year, p=0.028; height SDS change: 0.78 ± 0.39 vs. 0.61 ± 0.41, p<0.001). However, height SDS at 24 and 48 months were similar between groups. No significant differences in overall height velocity, annualized treatment continuation rate, and safety profile were observed over 48 months.

Conclusions: Weekly GH therapy appears to be an effective and safe alternative to daily GH treatment in children with GH deficiency over a 4-year period. Further research with larger sample sizes and longer follow-up is needed to confirm these findings and assess the extended safety and effectiveness of LAGH.

***Corresponding author: Hyo-Kyoung Nam**, MD, PhD, Department of Pediatrics, Korea University Guro Hospital, Korea University College of medicine, 148, Gurodong-ro, Guro-gu, Seoul, 08308, Korea,
E-mail: muguet@korea.ac.kr. https://orcid.org/0000-0003-1512-2062
Eungu Kang, Lindsey Yoojin Chung, Young-Jun Rhie and Kee-Hyoung Lee, Department of Pediatrics, Korea University College of Medicine, Seoul, Korea

Keywords: childhood growth hormone deficiency; growth hormone treatment; long-acting growth hormone; LG growth study; safety and effectiveness

Introduction

The long-term safety and effectiveness of recombinant human growth hormone (GH) therapy in children with GH deficiency (GHD) has been in evidence for over 35 years [1–6]. It induces linear growth and the attainment of an adult height that is equivalent to the target height. The effectiveness of GH treatment is determined by the diagnosis, the appropriate dose of GH, and patient compliance and persistence. The initial GH dose is determined by weight or body surface area, followed by individualized dosing according to the clinical response in combination with serum IGF-I levels, which are used to monitor compliance, efficacy, and safety of GH treatment [5–8]. If the response to treatment is insufficient, reassessment for other causes of short stature and non-adherence is recommended [7].

In early trials, the GH was given intramuscularly three days a week [9]. After a daily subcutaneous injection was reported to be as effective as the intramuscular injection and to be better tolerated by children, the daily injection of GH is used in the majority of cases [10]. The daily subcutaneous injection resembles a physiologic spontaneous pattern of GH secretion, which is a pulsatile and episodic pattern. However, it is a challenge to achieve maximum adherence with daily injections due to device limitations, injection pain, the inconvenience of daily injections, and the costs and insurance barriers [11, 12]. Treatment outcomes can be compromised by frequent missed doses and early treatment discontinuation. It may be possible to reduce the frequency of injections with the development of a long-acting GH analog (LAGH) for weekly, bi-weekly, or monthly injections. Ultimately, this has the potential to improve treatment outcomes through a reduction in injection burden and better adherence.

LAGH can be created in two ways: by creating a subcutaneous depot of native or modified GH that is slowly released into the circulation, or by enabling rapid absorption from the delivery site and delaying removal from the

circulation [13, 14]. Efficacy of LAGH in terms of growth rate and IGF-I increase was comparable to daily GH with a similar safety profile [15–17]. Still, there are few studies evaluating the long-term effectiveness and safety of LAGH [18]. The aim of this study is to compare the long-term effectiveness of weekly GH with daily GH in children with GH deficiency.

Materials and methods

Subjects

The patients with GHD and treated with GH for more than 6 months were selected from the "LG Growth Study", which is an observational Korean multi-center registry to evaluate the long-term safety and effectiveness of four GH products (LG Chem Ltd., Korea; Eutropin®, Eutropin® AQ and Eutropin® Pen, and Eutropin® Plus) (Figure 1.) [19]. GHD was defined as follows: 1) height below the third percentile according to the 2017 Korean National Growth Charts at baseline [20]; 2) two separate GH stimulation tests using insulin, clonidine, L-arginine, L-dopa, or glucagon; 3) a peak GH level <10 ng/mL in both tests. Of 1750 patients with GHD, those who treated GH for less than 6 months (n=348), those switching GH preparations, and those with insufficient auxological data were excluded. Finally, 966 patients with GHD who treated with daily GH (Eutropin®, Eutropin® AQ and Eutropin® Pen, n=773) or weekly GH (Eutropin® Plus, n=193) were included.

Written informed consent was obtained from all patients and their parents before participation in LGS, and the study was approved by the Institutional Review Board of Korea University Guro Hospital (IRB No. 2021GR0201).

Clinical data

The chronological age (CA), sex, mid-parental height (MPH), height, weight, Tanner stage, bone age (BA), the result of GH stimulation tests, insulin-like growth factor (IGF)-I, IGF-binding protein-3 (IGFBP-3), thyroid function test, serum glucose, lipid profile, GH dose, and adverse events were obtained at baseline and every 6 months from LGS database.

The standard deviation score (SDS) of height, weight, and body mass index were calculated using LMS parameters in the 2017 Korean National Growth Charts [20]. MPH was calculated by adding 6.5 cm for boys or subtracting 6.5 cm for girls from the average height of the parents and was converted to SDS values. BA was assessed by the Greulich-Pyle method [21]. As an observational study, all laboratory tests were performed according to standard procedures of each center. The timing of IGF-I measurements was not standardized, and the blood sampling took place on any day between injections when follow-ups. IGF-I and IGFBP-3 SDS were calculated using the age- and sex-specific Korean reference values [22]. The differences of clinical and laboratory data before and treatment was calculated as changes between the two values.

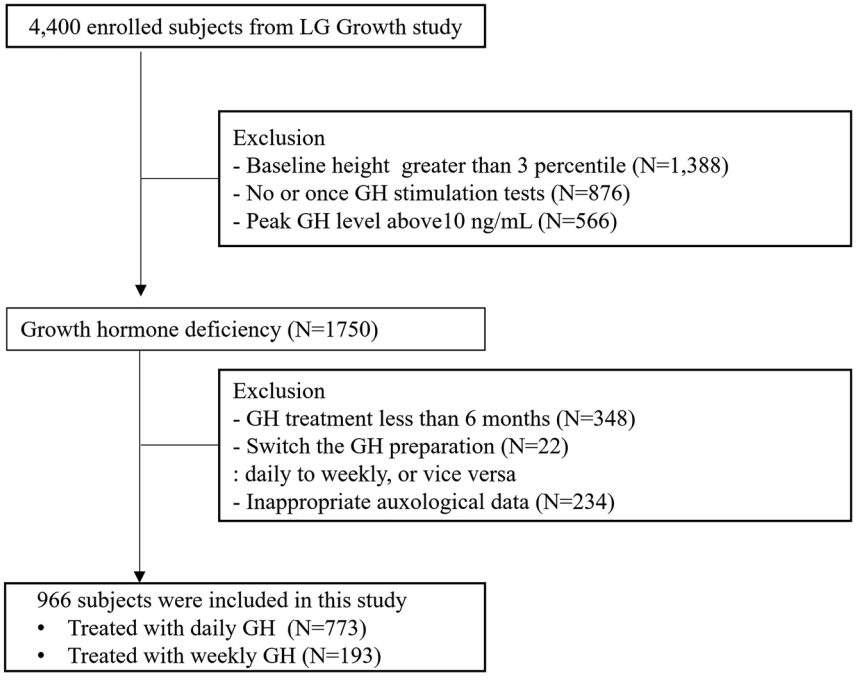

Figure 1: The flow chart of cohort.

Statistical analysis

Continuous variables were reported as mean and standard deviation and categorical variables were reported as frequency and proportion. The *t*-test was performed for comparison of continuous variables and chi-square test for categorical variables. Linear mixed model (LMM) was used to identify characteristics associated with height velocity. In the model, GH preparation (daily, weekly), age, gender, height/weight/BMI SDS, BA, IGF-1/IGFBP-3 SDS were included as fixed effect. To estimate the association between GH preparation and height velocity over treatment period, treatment period per GH preparation considered as a repeated effect. A p-value <0.05 was considered statistically significant. All statistical analyses were performed with SAS (SAS institute, version 9.4).

Results

Demographic and clinical characteristics of the patients

A total of 996 patients (773 daily GH and 193 weekly GH) were included in this study. The mean age before treatment was 7.66 ± 3.03 years, and 554 (55.62 %) were male. The characteristics at baseline are shown in Table 1. The average age at baseline was 7.5 ± 2.9 years in the daily group and 8.5 ± 3.4 year in the weekly group. There were no significant differences in baseline height SDS, weight SDS, BMI SDS, IGF-I, IGF-I SDS, difference of bone age and chronologic age, or peak GH value (all p>0.05). However, age, MPH-SDS, Tanner stage in males, IGFBP-3, and IGFBP-3 SDS showed significant differences between the two groups (Table 1). The mean GH dose of GH therapy were significantly higher in the weekly group than in the daily group (0.58 ± 0.17 mg/kg/week vs. 0.23 ± 0.05 mg/kg/week, p<0.001). The difference in duration of GH therapy between the two groups was not statistically significant (1,464.41 ± 850.75 days vs. 1,365.27 ± 875.24 days, p=0.157).

Effectiveness and adherence of weekly GH

Height SDS, change in height SDS, IGF-I, and IGF-I SDS were increased from baseline to 4 years in both group, although the height SDS and change in height SDS after 1 years of treatment were significantly greater in daily group (Table 2 and Figure 2A). Annualized height velocity after 1

Table 1: Baseline characteristics of children with GHD.

	Total (n=996)	Daily (n=773)	Weekly (n=193)	p-Value
Age, years	7.66 ± 3.03	7.46 ± 2.89	8.46 ± 3.44	<0.001
Male/female	554/441	435/337	119/74	0.182
Mid parental height SDS	−0.91 ± 0.75	−0.88 ± 0.73	−1.02 ± 0.84	0.044
Height SDS	−2.70 ± 0.70	−2.68 ± 0.71	−2.77 ± 0.66	0.111
Weight SDS	−1.86 ± 1.09	−1.86 ± 1.08	−1.87 ± 1.14	0.88
BMI SDS	−0.38 ± 1.13	−0.38 ± 1.12	−0.38 ± 1.17	0.995
Breast Tanner 1/Tanner 2–5 (n=260)	202/58	164/49	39/9	0.566
Testis volume, mL <4/≥4 (n=269)	215/54	182/37	33/17	0.006
IGF-I, ng/mL	141.01 ± 74.86	139.27 ± 72.71	148.08 ± 82.96	0.254
IGF-I SDS	−0.84 ± 0.83	−0.82 ± 0.85	−0.93 ± 0.75	0.152
IGFBP-3, ng/mL	2,768.81 ± 1,076.56	2,817.02 ± 1,109.81	2,529.53 ± 859.86	0.010
IGFBP-3 SDS	0.27 ± 2.10	0.44 ± 2.16	−0.58 ± 1.51	<0.001
Bone age, years	6.23 ± 3.05	6.02 ± 2.94	7.05 ± 3.36	<0.001
Bone age – chronological age, years	−1.93 ± 1.12	−1.94 ± 1.13	−1.88 ± 1.07	0.518
Peak GH after GH stimulation test, ng/mL	6.12 ± 2.50	6.16 ± 2.51	5.97 ± 2.45	0.369
GH dose, mg/kg/week	0.30 ± 0.17	0.23 ± 0.05	0.58 ± 0.17	<0.001
GH treatment total period, day	1,385.10 ± 870.87	1,365.27 ± 875.24	1,464.41 ± 850.75	0.157
TSH, μU/mL	2.91 ± 1.87	2.90 ± 1.83	2.94 ± 2.01	0.775
Total cholesterol, mg/dL	173.16 ± 30.07	172.93 ± 30.06	174.15 ± 30.23	0.704
Triglyceride, mg/dL	92.97 ± 47.50	91.08 ± 47.53	104.90 ± 46.62	0.216
Glucose, mg/dL	93.62 ± 15.12	93.49 ± 14.41	94.13 ± 17.68	0.674
HbA1c, %	5.40 ± 0.97	5.41 ± 1.12	5.35 ± 0.22	0.639

BA, bone age; BMI, body mass index; CA, chronological age; IGF-I, insulin like growth factor-I; IGFBP-3, insulin-like growth factor binding protein-3; GH, growth hormone; TSH, thyroid stimulating hormone.

Table 2: The treatment outcomes of both groups.

	After 6 ± 2 months			After 12 ± 2 months			After 24 ± 2 months		
	Daily (n=728)	Weekly (n=179)	p-Value	Daily (n=582)	Weekly (n=158)	p-Value	Daily (n=377)	Weekly (n=123)	p-Value
Height, cm	118.20 ± 14.84	121.63 ± 17.73	0.0178	121.80 ± 14.99	124.97 ± 18.34	0.0471	127.98 ± 15.49	131.69 ± 17.83	0.0406
Height SDS	−2.16 ± 0.68	−2.40 ± 0.76	<0.001	−1.95 ± 0.75	−2.20 ± 0.86	0.001	−1.60 ± 0.79	−1.75 ± 0.82	0.088
Weight SDS	−1.60 ± 0.96	−1.56 ± 1.14	0.634	−1.46 ± 0.98	−1.51 ± 1.24	0.680	−1.18 ± 1.03	−1.06 ± 1.12	0.288
BMI SDS	−0.52 ± 1.00	−0.30 ± 1.08	0.012	−0.55 ± 1.01	−0.38 ± 1.11	0.064	−0.47 ± 1.05	−0.22 ± 1.11	0.031
BA-CA, year	−1.24 ± 1.27	−1.29 ± 1.22	0.751	−1.07 ± 1.23	−1.17 ± 1.09	0.585	−0.88 ± 1.45	−0.90 ± 1.08	0.932
IGF-1, ng/mL	268.33 ± 139.59	290.83 ± 186.00	0.208	292.94 ± 149.17	344.87 ± 219.25	0.018	340.38 ± 178.58	387.50 ± 217.43	0.058
IGF-1 SDS	0.52 ± 1.41	0.47 ± 2.21	0.786	0.58 ± 1.40	0.60 ± 1.74	0.899	0.77 ± 1.54	1.06 ± 2.35	0.265
IGFBP-3, ng/mL	3,442.54 ± 1,356.79	3,116.54 ± 1,000.67	0.017	3,466.98 ± 1,501.63	3,189.38 ± 1,057.05	0.081	3,763.54 ± 1,586.22	3,394.14 ± 1,354.63	0.137
IGFBP-3 SDS	1.54 ± 2.58	0.32 ± 1.70	<0.001	1.39 ± 2.81	0.35 ± 1.76	0.000	1.71 ± 2.91	0.46 ± 2.20	0.001
TSH, μIU/mL	2.49 ± 1.48	2.57 ± 2.11	0.678	2.33 ± 1.41	2.62 ± 1.42	0.052	2.27 ± 1.32	2.41 ± 2.06	0.559
Total cholesterol, mg/dL	162.79 ± 26.47	169.25 ± 36.06	0.118	163.62 ± 28.11	167.40 ± 40.16	0.417	164.75 ± 29.10	162.26 ± 30.00	0.540
Triglycerides, mg/dL	115.96 ± 80.25	109.50 ± 43.76	0.823	104.13 ± 66.94	118.89 ± 30.77	0.262	114.88 ± 52.42	102.38 ± 41.40	0.518
Glucose, mg/dL	98.30 ± 13.01	97.13 ± 14.66	0.455	97.93 ± 12.20	97.86 ± 15.98	0.9710	97.19 ± 11.95	101.79 ± 22.50	0.1117
HbA1c, %	5.46 ± 2.73	5.34 ± 0.36	0.484	5.40 ± 1.82	5.31 ± 0.35	0.4712	5.51 ± 2.31	6.11 ± 4.52	0.4451

	After 36 ± 2 months			After 48 ± 2 months		
	Daily (n=232)	Weekly (n=83)	p-Value	Daily (n=165)	Weekly (n=65)	p-Value
Height, cm	133.55 ± 14.64	134.82 ± 17.23	0.5197	138.92 ± 14.59	138.36 ± 15.90	0.7995
Height SDS	−1.39 ± 0.85	−1.67 ± 1.08	0.034	−1.27 ± 0.93	−1.50 ± 1.28	0.194
Weight SDS	−0.97 ± 1.03	−1.08 ± 1.55	0.555	−0.87 ± 1.04	−0.99 ± 1.71	0.587
BMI SDS	−0.38 ± 1.10	−0.26 ± 1.35	0.483	−0.32 ± 1.10	−0.28 ± 1.31	0.827
BA-CA, year	−0.59 ± 1.42	−0.50 ± 1.58	0.743	−0.30 ± 1.56	−0.01 ± 1.30	0.463
IGF-1, ng/mL	375.59 ± 177.94	376.41 ± 188.17	0.972	416.32 ± 214.54	402.72 ± 182.84	0.673
IGF-1 SDS	0.96 ± 1.53	0.83 ± 1.89	0.570	1.00 ± 1.46	1.16 ± 1.72	0.489
IGFBP-3, ng/mL	3,819.03 ± 1,566.87	3,245.61 ± 1,074.10	0.008	3,610.57 ± 1,523.29	3,196.82 ± 1,113.05	0.196
IGFBP-3 SDS	1.63 ± 2.82	0.11 ± 1.72	<0.0001	1.00 ± 2.59	0.13 ± 1.99	0.116
TSH, μIU/mL	2.62 ± 6.90	2.46 ± 1.40	0.7467	2.13 ± 1.33	2.12 ± 1.20	0.978
Total cholesterol, mg/dL	161.08 ± 28.14	153.52 ± 23.33	0.0783	161.60 ± 31.45	157.97 ± 21.62	0.448
Triglycerides, mg/dL	102.33 ± 57.05	81.00 ± 36.31	0.469	102.36 ± 49.33	141.50 ± 89.80	0.312
Glucose, mg/dL	96.97 ± 11.83	98.20 ± 14.87	0.5809	94.54 ± 12.10	97.88 ± 13.13	0.1560
HbA1c, %	5.59 ± 2.65	5.43 ± 0.29	0.5448	5.30 ± 0.26	5.30 ± 0.36	1.0000

BA, bone age; BMI, body mass index; CA, chronological age; IGF-I, insulin like growth factor-I; IGFBP-3, insulin-like growth factor binding protein-3; GH, growth hormone; TSH, thyroid stimulating hormone.

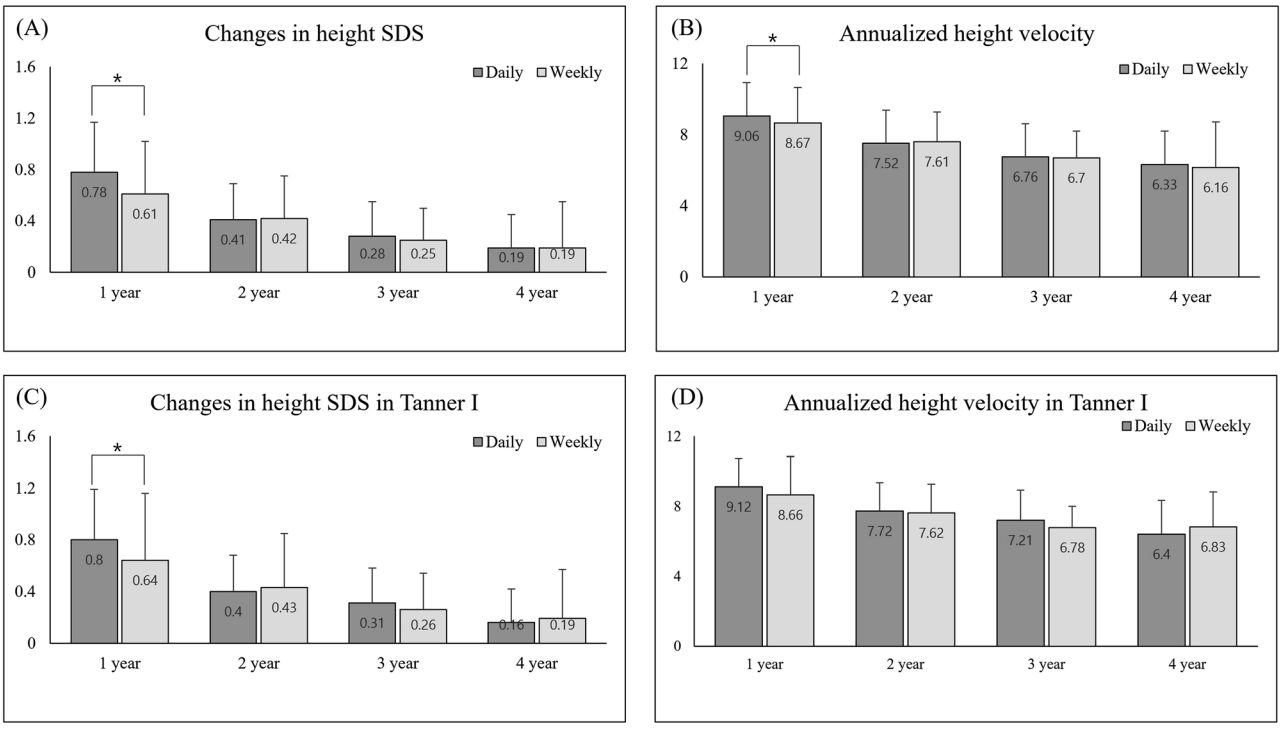

Figure 2: The change in height SDS and annualized height velocity during 4-year growth hormone treatment for both all patients (A, B) and for those who were Tanner I at baseline (C, D).

year treatment was 9.06 ± 1.72 cm/year in the daily group and 8.67 ± 1.98 cm/year in the weekly group (p=0.028). Height velocity decreased over time, and there were no significant differences in HV between two groups (Figure 2B). In linear mixed model analysis, the annualized height velocity showed no significant differences in the two groups considering the repeated measurements (Table 3). In addition, there was no significant difference in annual treatment continuation rates (Figure 3, p=0.717). The reasons for observation discontinuation were shown in Supplementary Table 1, most patients were lost to follow-up, while a minority discontinued GH treatment due to epiphyseal closure.

Subgroup analysis of effectiveness in patients with Tanner stage I at baseline and patients who treated with GH over 48 months.

A total of 529 patients (260 girls and 269 boys) had Tanner stating records at baseline. Among them, 77.69 % (n=202) of girls and 79.93 % (n=215) of boys were classified as Tanner stage I. Table 4 summarizes the clinical and laboratory findings of these patients at baseline and during follow-up. At baseline, the height SDS, IGF-I SDS, IGFBP-3 SDS were significantly low in weekly group. Height SDS and change in height SDS after 1 year of treatment was significantly greater in daily group (Figure 2C, –1.88 ± 0.67 vs. –2.21 ± 1.00, p=0.024 and 0.78 ± 0.39 vs. 0.61 ± 0.41, p=0.032, respectively). However, there were no significant differences in annualized height velocity, IGF-1 SDS, IGFBP-3 SDS after 1 year of treatment (Figure 2D).

Due to the significant reduction of patients over time, the subgroup was performed with the patients who had data available at 48 months after treatment, including 165 patients on daily GH and 65 patients on weekly GH. At baseline, the IGFBP-3 SDS was significantly lower in weekly group, however, there were no significant differences in height SDS or IGF-1 SDS during treatment (Supplementary Table 2).

Safety of weekly GH

There were no significant adverse events observed during the observation period in both groups. The majority of measured IGF-1 SDS remained within normal limits. There were no significant differences in IGF-1 SDS, TSH, total cholesterol, and glucose profile in both group (Table 5, all p>0.05).

Table 3: Factors affecting height velocity.

Variables	Dependent variable: Height velocity, cm/year		
	β, parameter estimate	Standard error	p-Value
Intercept	12.651	0.560	<0.0001
GH preparation (ref: weekly)			
Daily	0.006	0.480	0.9895
Age, years	−0.019	0.029	0.5035
Gender (ref: female)	−0.013	0.113	0.9048
Height SDS	1.366	0.164	<0.0001
Weight SDS	−0.348	0.297	0.2420
BMI SDS	0.291	0.231	0.2073
Bone age, years	0.079	0.025	0.0014
GH dose	−1.016	0.430	0.0186
IGF-1 SDS	0.018	0.018	0.3105
IGFBP-3 SDS	−0.022	0.013	0.0896
Treatment periods			
6 months	Ref		
12 months	−0.892	0.437	0.0416
18 months	−1.568	0.432	0.0003
24 months	−1.968	0.420	<0.0001
30 months	−2.677	0.426	<0.0001
36 months	−3.154	0.423	<0.0001
42 months	−3.572	0.428	<0.0001
48 months	−4.165	0.420	<0.0001
Repeated variables (ref: weekly)			
Daily*6 months	Ref		
Daily*12 months	−0.466	0.462	0.3135
Daily*18 months	−0.588	0.453	0.1949
Daily*24 months	−0.723	0.437	0.0989
Daily*30months	−0.442	0.441	0.3165
Daily*36months	−0.346	0.436	0.4285
Daily*42 months	−0.231	0.439	0.5985
Daily*48 months	0.037	0.428	0.9303

BMI, body mass index; IGF-I, insulin like growth factor-I; IGFBP-3, insulin-like growth factor binding protein-3; GH, growth hormone; TSH, thyroid stimulating hormone.

Discussion

There are few studies of the long-term effectiveness and safety of LAGH treatment in children with GHD. This study evaluates the long-term effectiveness and safety of weekly growth hormone (GH) therapy compared to daily GH therapy in children with GH deficiency. The results suggest that over a 4-year treatment period, weekly GH treatment is comparable to daily GH treatment in terms of height improvement, annualized height velocity, and various growth-related parameters. The study also indicates that treatment adherence rates were similar between the daily and weekly groups. To the best of our knowledge, this is the first report of real-world evidence of the effectiveness and safety of LAGH, with the longest follow-up period in LAGH.

The efficacy and safety of LAGH preparations was confirmed in clinical trials, and some have been approved for pediatric GHD [23–25]. Eutropin® Plus (LB03002) was approved in South Korea in 1992 and in Europe 2013, but not marketed in Europe. Eutropin® Plus is a depot formulation of sodium hyaluronate microparticles containing GH and dispersed in an oily base of medium-chain triglycerides. The microparticles are degraded by tissue hyaluronidase, which allows sustained GH release. The efficacy and safety of LB03002 have been reported in several clinical trials [15–17].

A 3-year randomized, controlled, multicenter, phase 2/3 studies in prepubertal children with GHD showed that the dose of 0.5 mg/kg/week and 0.7 mg/kg/week were as effective as daily dose of 0.03 mg/kg/day [16]. The growth velocity of children receiving a dose 0.5 mg/kg/week of LB03002 was 11.75 ± 1.88 cm/year in the first 12 months, 9.89 ± 1.45 cm/year in the second year, and 9.01 ± 1.33 cm/year in the third year, which were all greater than those observed in our registry. In our study, the mean weekly

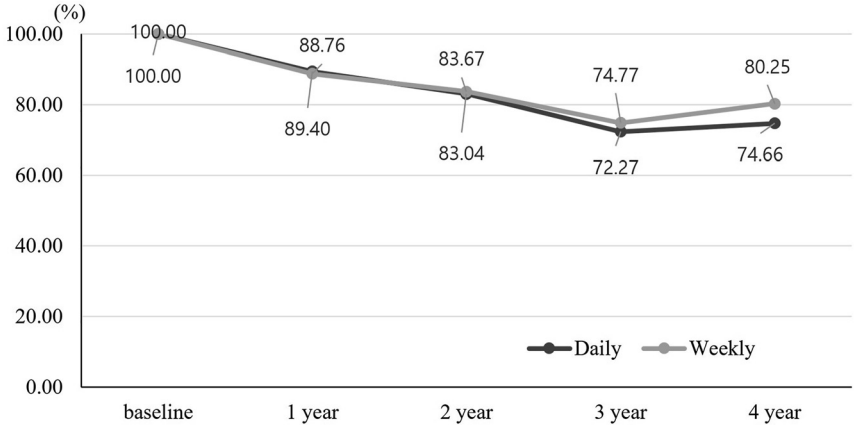

Figure 3: Annualized GH treatment continuation rate.

Table 4: Treatment outcomes in children with Tanner I at baseline.

	Baseline			After 12 months ± 2 months			After 24 months ± 2 months		
	Daily (n=346)	Weekly (n=71)	p-Value	Daily (n=264)	Weekly (n=57)	p-Value	Daily (n=169)	Weekly (n=46)	p-Value
Age, years	7.23 ± 2.57	8.14 ± 3.51	0.040	8.28 ± 2.61	8.82 ± 3.67	0.2875	9.18 ± 2.73	9.93 ± 3.67	0.2008
MPH SDS	−0.93 ± 0.73	−0.92 ± 0.73	0.920	–	–	–	–	–	–
Height SDS	−2.62 ± 0.56	−2.81 ± 0.67	0.027	−1.88 ± 0.67	−2.21 ± 1.00	0.024	−1.54 ± 0.70	−1.66 ± 0.81	0.315
Weight SDS	−1.76 ± 0.98	−1.87 ± 1.14	0.419	−1.38 ± 0.94	−1.61 ± 1.33	0.225	−1.03 ± 0.96	−1.17 ± 0.93	0.364
BMI SDS	−0.33 ± 1.11	−0.34 ± 1.21	0.951	−0.51 ± 1.01	−0.47 ± 1.04	0.776	−0.35 ± 1.08	−0.42 ± 0.95	0.718
BA-CA, years	−2.06 ± 1.13	−1.88 ± 1.07	0.216	−1.13 ± 1.18	−1.52 ± 1.19	0.159	−0.78 ± 1.52	−0.87 ± 1.12	0.795
IGF-1, ng/mL	137.68 ± 70.39	130.50 ± 64.66	0.487	292.71 ± 131.13	336.33 ± 188.89	0.155	341.81 ± 164.21	371.82 ± 208.07	0.368
IGF-1 SDS	−0.75 ± 0.92	−1.09 ± 0.72	0.004	0.73 ± 1.49	0.58 ± 1.71	0.544	0.80 ± 1.52	0.65 ± 1.60	0.605
IGFBP-3, ng/mL	2,810.76 ± 1,070.18	2,572.82 ± 819.99	0.219	3,517.36 ± 1,549.54	3,380.72 ± 1,138.43	0.685	3,709.48 ± 1,502.69	3,905.19 ± 1,664.10	0.609
IGFBP-3 SDS	0.53 ± 2.18	−0.54 ± 1.42	0.001	1.50 ± 2.91	0.73 ± 2.10	0.221	1.53 ± 2.72	1.34 ± 2.73	0.776
TSH, μIU/mL	2.97 ± 1.77	3.16 ± 2.50	0.579	2.46 ± 1.39	2.47 ± 1.42	0.989	2.41 ± 1.42	2.25 ± 1.51	0.551
Total cholesterol, mg/dL	171.93 ± 30.52	170.14 ± 31.63	0.750	160.54 ± 25.61	166.10 ± 30.21	0.294	160.75 ± 27.11	157.52 ± 29.97	0.599
Triglycerides, mg/dL	91.21 ± 44.63	95.13 ± 20.50	0.680	96.62 ± 65.90	94.33 ± 4.16	0.838	104.00 ± 36.09	80.50 ± 19.09	0.375

	After 36 months ± 2 months			After 48 months ± 2 months		
	Daily (n=90)	Weekly (n=31)	p-Value	Daily (n=73)	Weekly (n=23)	p-Value
Age, years	10.24 ± 2.71	9.65 ± 3.05	0.3058	11.14 ± 2.45	9.61 ± 2.57	0.0115
MPH SDS	–	–	–	–	–	–
Height SDS	−1.25 ± 0.75	−1.68 ± 1.32	0.098	−1.17 ± 0.83	−1.83 ± 1.90	0.118
Weight SDS	−0.87 ± 0.94	−1.23 ± 1.67	0.268	−0.70 ± 0.97	−1.61 ± 2.19	0.065
BMI SDS	−0.37 ± 1.05	−0.39 ± 1.29	0.921	−0.19 ± 1.12	−0.74 ± 1.09	0.039
BA-CA, years	−0.32 ± 1.55	−0.44 ± 1.81	0.810	−0.17 ± 1.71	0.12 ± 1.56	0.617
IGF-1, ng/mL	395.66 ± 193.82	368.34 ± 188.25	0.502	454.63 ± 223.22	415.85 ± 224.79	0.481
IGF-1 SDS	1.09 ± 1.59	0.59 ± 1.37	0.124	1.16 ± 1.53	1.15 ± 1.85	0.982
IGFBP-3, ng/mL	3,841.79 ± 1,591.78	3,478.29 ± 1,368.64	0.411	3,542.99 ± 1,336.74	2,931.23 ± 530.83	0.039
IGFBP-3 SDS	1.65 ± 2.83	0.61 ± 2.07	0.181	0.80 ± 2.35	−0.31 ± 0.67	0.012
TSH, μIU/mL	3.44 ± 10.56	2.38 ± 1.51	0.364	2.40 ± 1.39	1.83 ± 1.21	0.096
Total cholesterol, mg/dL	158.53 ± 31.84	154.87 ± 25.78	0.624	158.95 ± 31.06	155.76 ± 23.25	0.703
Triglycerides, mg/dL	100.36 ± 73.73	54	0.561	86.14 ± 17.56	–	–

BA, bone age; BMI, body mass index; CA, chronological age; IGF-I, insulin like growth factor-I; IGFBP-3, insulin-like growth factor binding protein-3; GH, growth hormone; TSH, thyroid stimulating hormone.

Table 5: Safety of weekly growth hormone compared to daily growth hormone in children with growth hormone deficiency.

		6 months			12 months			24 months		
		Daily	Weekly	p-Value	Daily	Weekly	p-Value	Daily	Weekly	p-Value
IGF-1 SDS[a]	<−2	10 (1.68 %)	3 (2.46 %)	0.843	5 (1.07 %)	1 (0.88 %)	0.905	4 (1.22 %)	0 (0.00 %)	0.2348
	≥−2 and ≤+2	520 (87.54 %)	106 (86.89 %)		400 (85.29 %)	99 (86.84 %)		267 (81.65 %)	71 (76.34 %)	
	>+2	64 (10.77 %)	13 (10.66 %)		64 (13.65 %)	14 (12.28 %)		56 (17.13 %)	22 (23.66 %)	
HbA1c, %	≤6.00 %	664 (99.55 %)	181 (98.91 %)	0.294	583 (99.83 %)	177 (99.44 %)	0.413	430 (99.54 %)	154 (98.72 %)	0.2875
	>6.0 %	3 (0.45 %)	2 (1.09 %)		1 (0.17 %)	1 (0.56 %)		2 (0.46 %)	2 (1.28 %)	
TSH, μIU/mL	<5	638 (95.65 %)	175 (95.63 %)	0.989	564 (96.58 %)	172 (96.63 %)	0.972	416 (96.30 %)	151 (96.79 %)	0.7736
	≥5	29 (4.35 %)	8 (4.37 %)		20 (3.42 %)	6 (3.37 %)		16 (3.70 %)	5 (3.21 %)	
Total cholesterol, mg/dL	<200	638 (95.65 %)	176 (96.17 %)	0.756	549 (94.01 %)	171 (96.07 %)	0.292	409 (94.68 %)	152 (97.44 %)	0.1580
	≥200	29 (4.35 %)	7 (3.83 %)		35 (5.99 %)	7 (3.93 %)		23 (5.32 %)	4 (2.56 %)	

		36 months			48 months		
		Daily	Weekly	p-Value	Daily	Weekly	p-Value
IGF-1 SDS[a]	<−2	6 (2.65 %)	1 (1.25 %)	0.755	2 (1.29 %)	1 (1.79 %)	0.526
	≥−2 and ≤+2	175 (77.43 %)	62 (77.50 %)		115 (74.19 %)	38 (67.86 %)	
	>+2	45 (19.91 %)	17 (21.25 %)		38 (24.52 %)	17 (30.36 %)	
HbA1c, %	≤6.00 %	315 (99.68 %)	125 (99.21 %)	0.489	223 (100.00 %)	85 (100.00 %)	NA
	>6.0 %	1 (0.32 %)	1 (0.79 %)		0 (0.00 %)	0 (0.00 %)	
TSH, μIU/mL	<5	308 (97.47 %)	123 (97.62 %)	1.000	218 (97.76 %)	83 (97.65 %)	1.000
	≥5	8 (2.53 %)	3 (2.38 %)		5 (2.24 %)	2 (2.35 %)	
Total cholesterol, mg/dL	<200	306 (96.84 %)	125 (99.21 %)	0.191	214 (95.96 %)	85 (100.00 %)	0.068
	≥200	10 (3.16 %)	1 (0.79 %)		9 (4.04 %)	0 (0.00 %)	

[a]The timing of IGF-I, measurements took place on any day between injections when follow-ups. IGF-I, insulin like growth factor-I; TSH, thyroid stimulating hormone.

GH dose and daily GH dose were 0.58 ± 0.17 mg/kg/week and 0.23 ± 0.05 mg/kg/week, respectively, which were slightly higher than phase 2/3 study. Although the growth velocity of the weekly group in our study was lower than that of the clinical trial, it was comparable to the daily group and showed significant improvement in height SDS during treatment. In our study, the changes in height SDS were higher in the daily group until 12 months after treatment, whereas the change in height SDS from baseline was not significantly different after 24 months of treatment. The height velocity and height SDS improvement from baseline in both treatment groups observed in our study were comparable to the long-term effectiveness of GH treatments of GHD [18, 26, 27].

The benefits of once-weekly preparations can reduce the number of injections and the treatment burden, thereby improving treatment adherence, helping patients continue treatment, and improving quality of life [28]. Since this observational study has limitations, we could not confirm whether patients adhered to the number of injections. However, there was no difference in annual treatment continuation rates between the daily and weekly groups. Recent meta-analysis reported that the treatment adherence in LAGH was high (92.2–99.6 %) and it was comparable with daily GH (87.2–99.7 %) [27]. The studies included in this meta-analysis was clinical trial, the high levels of adherence may not be generalized in a real-world setting and further long-term observational studies are required.

Adverse events associated with LAGH were similar in incidence and were mostly mild to moderate in intensity and transient [27]. The most common adverse events reported were injection site reactions. Also, as consistent with the results of this study, fasting glucose, HbA_{1c}, and thyroid function remained unchanged from baseline to the end of follow-up between the long-acting GH and daily GH groups. GH regulates fat and glucose metabolism, body composition, and other body functions [29, 30]. The short-term metabolic response to continuous infusion of GH over 6 months was comparable to intermittent GH exposure in terms of serum IGF-1, insulin sensitivity, lipoprotein, bone metabolism, and body composition [31]. However, concerns remain about the long-term effects of prolonged elevated GH and IGF-I levels, which can lead to long-term metabolic problems.

Serum IGF-I levels reflect the efficacy, adherence, and safety in LAGH treatment, and are commonly used to monitor GH effects [32]. Although there is little evidence of a safe upper limit of serum IGF-I levels, the avoidance of exposure to supra-physiologic IGF-I levels for too long is important as this could increase risk of neoplasia, acromegaly and glucose intolerance [5]. Conversely, the insufficient IGF-I levels result in suboptimal growth outcomes. The IGF-I response to long-acting GH differs from daily GH and from each other, depending on their bioavailability and administered dose [33, 34]. The peak IGF-I level was achieved 36–72 h after administration of LB03002 [35]. LGS database did not record the time points of IGF-I measurements, which limits the interpretation of whether appropriate IGF-I levels were achieved for effectiveness and safety. Better understanding of the pharmacokinetic and pharmacodynamic profiles of each LAGH is needed to determine the optimal timing for serum IGF-I measurement and dose adjustments based on IGF-I levels. This will enable the development of proper guidelines for IGF-I monitoring in specific to each LAGH.

While this study highlights the potential benefits of weekly GH therapy and reports no significant adverse events during the observation period, it acknowledges certain limitations, such as a small sample size with a decreased number of patients after 4 years, incomplete information on pubertal stage, and the need for longer-term observations to assess the extended safety and effectiveness of treatment.

In summary, the study contributes to our understanding of the use of LAGH in the treatment of GH deficiency in children. However, further research with larger sample sizes and longer follow-up periods is necessary to confirm these findings and to address potential long-term effects and rare adverse events associated with this treatment approach.

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