Long-Term Efficacy and Safety of Recombinant Human Growth Hormone in Children Born Small for Gestational Age

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Keywords

growth disorder, HT-SDS, height velocity, gestational age

received 17.01.2023
accepted after revision 13.07.2023

Bibliography

Horm Metab Res 2023; 55: 599–609
DOI 10.1055/a-2136-8654
ISSN 0018-5043

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Supplementary material is available under https://doi.org/10.1055/a-2136-8654.

ABSTRACT

There is a lack of long-term data on the benefit of growth hormone (GH) treatment in Chinese children born small for gestational age (SGA). This study was conducted to assess the long-term efficacy and safety of GH treatment in children born SGA. One hundred and twenty prepubertal SGA children who did not achieve catch-up growth with height remained less than –2 standard deviations (SD) below gender-specific height were enrolled in this two-year, randomized, dose-comparative study followed by an extension study of up to 10 years. Daily subcutaneous injections of 0.23 mg/kg/week [low-dose (LD) group] or 0.46 mg/kg/week [high-dose (HD) group] somatropin were given for 104 weeks. Dosing in the extension study was ≤ 0.46 mg/kg/week. The main outcome measures were change in height SD score (ΔHT-SDS), height velocity, insulin-like growth factor (IGF)-1, and IGF-1/IGF binding protein-3 (IGFBP-3) molar ratio. ΔHT-SDS at week 104 was 0.91 ± 0.53 and 1.52 ± 0.64 in the LD and HD groups (intergroup $p < 0.0001$), respectively, and continued in an upward trend throughout the extension study, remaining above + 2 for those who received treatment for a total of 7 years or more. At week 104, significant improvements were observed in height velocity, IGF-1 SDS, and IGF-1/IGFBP-3 molar ratio. Adult HT-SDS was –0.81 ± 1.68 for boys and –0.82 ± 1.05 for girls ($p = 0.9837$). Glucose metabolism and thyroid function were within the normal reference range throughout treatment. Long-term recombinant human GH treatment was tolerable and effective at improving height in children born SGA.

Introduction

Small for gestational age (SGA) is commonly defined as a birth weight and/or length less than two standard deviations (SDs) below the mean for gestational age [1]. Globally, it was estimated in 2010 that 32.4 million babies, constituting 27 % of the total births in low- and middle-income countries, were born SGA [1]. Suboptimal body size increases the risk for cardiovascular diseases, hypertension, and type 2 diabetes mellitus, among others, as long-term complications [2].

Although most infants born SGA achieve spontaneous catch-up growth during the early stages of life by age 2 years, a substantial proportion, around 10–15 %, remain short as adults [3]. Recombinant human growth hormone (rhGH) was approved in the United States and Europe in 2001 for treatment of SGA children who fail to achieve catch-up growth [4, 5]. Continuous therapy with daily rhGH for 2 years or longer has been shown to improve height gain, accelerate height velocity (HV), and result in an adult height within the genetically predicted range [6–10]. According to a longitudinal observational study on young adults born SGA, long-term rhGH treatment not only did not impact negatively on cardiovascular health but also improved lipid profiles [11].

While a good safety profile was, overall, demonstrated in SGA children who were treated with rhGH, regular monitoring of glucose metabolism is needed, since GH treatment may reversibly exacerbate insulin resistance in this vulnerable population predisposed to reduced insulin sensitivity [8–10]. According to the findings of two Japanese studies, blood glucose concentrations were unaltered, whereas levels of glycosylated hemoglobin A1c (HbA1c) were slightly increased during the initial 2 years of rhGH therapy, but remained clinically non-relevant until 5 years of rhGH therapy [7, 9]. A significant rise in fasting and glucose-stimulated insulin levels were observed following 1 to 6 years of GH treatment, which returned to the normal range at 6 months after treatment discontinuation [10, 12]. In a study by Van der Steen et al., children with SGA were followed for up to 5 years after cessation of rhGH therapy; at a mean age of 21 years, it was found that there was no elevated fasting glucose and insulin concentration compared with those born appropriately sized for gestational age [11]. No diabetes mellitus was reported in these long-term studies [7, 9–12]. Decreased thyroxine levels, in terms of free thyroxine (FT4) concentrations, were revealed in children with GH deficiency (GHD) who received rhGH treatment [13, 14]. Persistent reduction in thyroxine induced by GH treatment could result in a poorer response to treatment and, hence, impact growth outcomes [13, 15]. Based on the limited evidence available for SGA children, mild, transient, and reversible alterations in serum FT4 that did not impact treatment response were observed after 2 years of rhGH treatment [14, 15].

In China, prevalence of SGA was estimated to be around 6.5–10.2 % [16, 17]. Most of the domestic studies investigating the treatment effect of rhGH on SGA children were single-center, short-term studies with small sample sizes. There is a lack of data on the regular monitoring of carbohydrate metabolism and thyroid function during the treatment period, and long-term findings on the effectiveness and safety of rhGH were also absent in Chinese children born SGA. Somatropin (Jintropin, GeneScience Pharmaceuticals, Changchun, China) is a daily rhGH therapy approved by the Chinese National Medical Products Administration (NMPA) for the treatment of various growth disorders with demonstrated efficacy and safety. Most recently, Jintropin showed clinical benefit in idiopathic short stature and Prader–Willi syndrome [18, 19]. Here, we report the findings of our multicenter study to evaluate growth, tolerability, and metabolic profiles of Chinese children born SGA treated with two different doses of rhGH over a 2-year period. Continuous follow-up data of up to 10 years were also retrieved to assess the long-term outcomes of daily rhGH in these children.

Subjects and Methods

Study design and subjects

This study consists of a 2-year, dose-comparative phase followed by an extension period of up to 10 years to demonstrate the efficacy and safety of rhGH (somatropin, Jintropin) in short stature children born SGA. Patients were recruited at five clinical sites in China from March 2010 to December 2012 and were randomized 1:1 to receive daily subcutaneous injections of either 0.23 mg/kg/week [low-dose (LD) group] or 0.46 mg/kg/week [high-dose (HD) group] somatropin for 104 weeks. Treatment was continued beyond week 104 at a dose not higher than 0.46 mg/kg/week if, at investigator's discretion, there would be prolonged benefit for the patient. Data were collected up to 2021 for the purpose of analyzing the long-term outcomes associated with rhGH treatment.

Children who were clinically diagnosed with SGA, defined as a birth weight below the tenth percentile of gestational age using the Chinese reference population (the corrected percentile of the birth weight of male and female newborns by gestational age from 15 cities in China) [20], were enrolled based on the following criteria: 1) chronological age (CA) of 2–6.5 years in girls and 2–7.5 years in boys; 2) prepubertal stage (Tanner stage 1); 3) without catch-up growth within 2 years from birth (catch-up growth is defined as a height reaching at least the third percentile of children of the same age and gender, in reference to the 2005 physical development survey of children aged 0–18 years in nine cities in China) [21]; 4) height lower than −2 SDs of normal children of the same age and gender (refer to the 2005 physical development survey of children aged 0–18 years in nine cities in China) [21]; 5) a GH peak concentration of > 10 ng/l in a provocative test within a year; 6) bone age (BA) < CA + 1; 7) fasting blood glucose < 5.6 mmol/l and 2-hour post-prandial blood glucose < 7.8 mmol/l; 8) gestational age ≥ 36 weeks + 4 days; and 9) never received GH treatment. Patients were excluded if they had any of the following conditions: liver and/or renal insufficiency (alanine aminotransferase > 2 × the upper limit of normal value, creatinine > upper limit of normal value); positive antibodies to hepatitis B core, hepatitis B surface antigen, or hepatitis B e antigen; known/suspected allergy or hypersensitivity to GH products; chronic diseases (diabetes, severe cardiopulmonary and pulmonary disease, hematological diseases, malignant tumors); systemic infection; immunocompromised; psychosis; or with any other type of growth and development disorder, such as Turner syndrome, constitutional delay of puberty, and Laron syndrome.

The study was conducted in compliance with the requirements of the Declaration of Helsinki and Good Clinical Practice of the NMPA in China. Before the start of the trial, the study protocol was reviewed by the Medical Ethics Committee of Tongji Medical School

of Huazhong University of Science and Technology. The study protocol and all amendments were also reviewed and approved by the Ethics Committee of each participating site. Written informed consents were obtained from all study patients or their guardian(s).

Statistical analysis

Efficacy was analyzed in the full analysis set (FAS) consisting of all randomized patients who had used rhGH at least once and had post-dose evaluation data. A safety analysis was performed on the safety set (SS) including all randomized patients who had at least one treatment and safety record.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Graphs were drawn using GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA). Continuous data were presented as mean ± SD and categorical data as frequency and percentage. Within-group comparisons before and after treatment were assessed using a paired *t*-test for parametric and a Wilcoxon signed-rank test for non-parametric continuous data. Intergroup comparisons were made using analyses of covariance with baseline results as the covariate, taking the center effect into account. Between-group comparisons of categorical data were conducted using Chi-squared or Fisher's exact tests. Correlations of insulin-like growth factor 1 (IGF-1) SD score, IGF-1/IGF binding protein-3 (IGFBP-3) molar ratio, and their corresponding changes from baseline with first and second year of treatment response (change in height SD score [ΔHT-SDS]) were also analyzed. A p-value < 0.05 was considered statistically significant.

Outcomes and assessments

Growth evaluations consisted of HT-SDS by CA and the corresponding change from baseline (ΔHT-SDS), evolution of height at the end of treatment, annual HV, serum IGF-1 and IGF-1/IGFBP-3 molar ratio, bone maturation, and rates of overweight or obesity. The definitions and calculations of the growth outcomes are listed in the Supplementary Information. Safety assessments included vital signs (blood pressure, heart rate, body temperature, and respiratory rate), electrocardiogram (ECG), hematology, urinalysis, blood biochemistry assays (liver function, renal function, lipids), HbA1c, fasting insulin (FINS), fasting plasma glucose (FPG), oral glucose tolerance tests (OGTT), thyroid function [TT4, TT3, and thyroid-stimulating hormone (TSH)], and incidence of adverse events (AEs).

At baseline, karyotype examination (in girls only, to exclude Turner syndrome), pituitary magnetic resonance imaging, and GH stimulation tests were conducted to rule out any growth disorders other than SGA. Auxological measurements of height, weight, head circumference, and Tanner stage were performed at baseline and weeks 4, 13, 26, 39, 52, 65, 78, 91, and 104, along with the assessment of vital signs, thyroid function, and serum IGF-1 and IGFBP-3 concentrations. BA X-ray, ECG, hematology, urinalysis, blood biochemistry assays, FINS, FPG, and anti-human GH (hGH) antibodies were examined at baseline and weeks 26, 52, 78, and 104. Every 3 months during the extended follow-up period from week 104 onwards there was continued monitoring of height, weight, glycemic parameters (FINS, FPG, HbA1c), and thyroid function. OGTTs were scheduled at baseline, weeks 52 and 104, and every 6 months thereafter, while in other visits they were conducted when impaired fasting glucose was indicated (FPG ≥ 5.6 mmol/l).

Height was normalized according to age and gender of the Chinese pediatric population [21]. A patient was considered to reach adult height (AH) if, during the last 6 months, their annual HV was less than 1 cm/year (height gain < 0.5 cm in the last 6 months). Bone maturation was expressed as the ratio of BA to CA with BA determined using the Tanner–Whitehouse 3 method. Overweight was defined as a body mass index (BMI) ≥ 85 % but < 95 % of the age- and gender-referenced population, and a BMI ≥ 95 % was classified as obesity [21]. Throughout the study, height and weight were measured at each clinical site using a designated weighing scale (RGZ-120; Jiangsu Deliberate Technology Co., Ltd, Changzhou, China) and height-measuring device (SZG-180; Nantong Bei Si Te Industry and Trade Co., Ltd, Nantong, China). The average of three measurements was taken as final. Serum samples from IGF-1, IGFBP-3, and anti-hGH antibodies testing that were collected and stored below –20 °C at each clinical site were sent on a regular basis to the Pediatrics Department of Tongji Hospital and Beijing North China Institution of Biotechnology (Beijing, China) for analysis.

Results

Patient disposition and baseline characteristics

A total of 120 patients were allocated to receive LD (n = 60) or HD (n = 60) rhGH (▶ **Fig. 1**). Among these, 117 and 118 patients were included in the FAS and SS, respectively. The baseline characteristics of the patients are presented in ▶ **Table 1**. Seventy-one boys (LD: 36; HD: 35) and 46 girls (LD: 23; HD: 23) in total were in the FAS. The mean CAs on study admission were 4.77 ± 1.16 and 4.66 ± 1.27 years in the LD and HD groups, respectively. In both groups, the mean HT-SDS was below –2 SDs of normal children. Compared with the HD group, marginally significantly higher IGF-1/IGFBP-3 was seen in the LD group (0.10 ± 0.03 vs. 0.09 ± 0.04; p = 0.043). No statistical difference in other demographic or baseline auxologic data were observed.

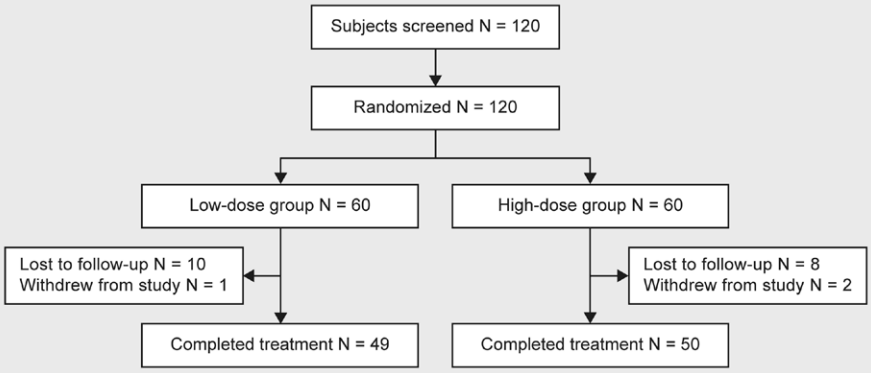
Sixty-eight patients who continued to receive treatment after 104 weeks were followed up for a mean duration of 43.6 months, during which 30 patients reached AH. Nineteen patients stopped treatment after less than 1 year, while 29 continued receiving treatment for more than 5 years.

HT-SDS and ΔHT-SDS

At week 104, mean HT-SDS was –1.86 ± 1.18 and –1.37 ± 1.24 in the LD and HD groups, respectively (▶ **Fig. 2a**). ΔHT-SDS from baseline was 0.91 ± 0.53 and 1.52 ± 0.64 in the LD and HD groups (intergroup p < 0.0001), respectively (▶ **Fig. 2b**). In both groups, compared with baseline, HT-SDS was statistically significant for all evaluable time points after initiation of treatment (p < 0.0001); ΔHT-SDS in the HD group was also significantly higher than in the LD group for all evaluable time points apart from week 13.

Height

At week 104, mean heights of children in the LD and HD groups were 112.6 ± 8.1 cm and 114.4 ± 10.0 cm, respectively, significantly higher



▶ **Fig. 1** Patient enrollment flow chart.

compared with baseline ($p < 0.0001$). The Δ heights at week 104 were 16.4 ± 2.2 cm and 19.6 ± 2.6 cm in the LD and HD groups, respectively ($p < 0.0001$). At all evaluable time points, Δ height was significantly higher in the HD group than in the LD group (▶ **Fig. 2c**).

HV

The mean annualized HVs of the LD and HD groups were 7.8 ± 1.2 cm/year and 9.4 ± 1.2 cm/year, respectively, after 104 weeks of treatment ($p < 0.0001$). HV in the HD group was significantly higher than in the LD group at all evaluable time points except week 4 (▶ **Fig. 2d**).

ΔBA/ΔCA

A stable trend for bone maturation (ΔBA/ΔCA) was reflected during the course of rhGH treatment. Throughout the study, ΔBA/ΔCA was slightly higher in the HD group than the LD group, but not statistically significant; at week 104, ΔBA/ΔCA in the HD and LD groups was 1.29 ± 0.31 and 1.27 ± 0.38 ($p = 0.8160$), respectively (▶ **Fig. 2e**).

IGF-1 SDS

IGF-1 SDS showed a rapid increase in the first 4 weeks, before plateauing from week 65 onwards and decreasing slightly at week 104. Significant increases in IGF-1 SDS were observed at all time points from baseline with GH treatment regardless of dose ($p < 0.0001$; ▶ **Fig. 2f**). During the course of treatment, Δ IGF-1 SDS remained consistently higher in the HD group than in the LD group ($p < 0.05$), though IGF-1 SDS at each time point suggested no statistical difference between the two groups. The mean IGF-1 SDS in the HD group remained more than + 2 from week 52 onwards (62.3 %, 65.4 %, 66.7 %, 60.0 %, and 52.0 % of patients had IGF-1 > + 2 SDS at weeks 52, 65, 78, 91, and 104, respectively).

IGF-1/IGFBP-3 molar ratio

IGF-1/IGFBP-3 molar ratio increased significantly from baseline at all evaluable time points ($p < 0.0001$; ▶ **Fig. 2g**). By week 104, IGF-1/IGFBP-3 molar ratios were 0.17 ± 0.05 and 0.21 ± 0.08 in the LD and HD groups, respectively. Compared with the LD group, a higher change from baseline was shown in the HD group (0.07 ± 0.05 vs. 0.12 ± 0.08; $p < 0.001$).

Correlations of IGF-1 SDS, IGF-1/IGFBP-3 molar ratio, and their corresponding changes from baseline with treatment response (ΔHT-SDS)

As seen in ▶ **Table 2**, in both groups, no significant correlation was found between ΔHT-SDS and any of IGF-1 SDS, ΔIGF-1 SDS, IGF-1/IGFBP-3 molar ratio, and ΔIGF-1/IGFBP-3 molar ratio after 1 year of rhGH treatment. At 2 years, ΔIGF-1 SDS in the HD group was significantly and positively correlated with ΔHT-SDS ($r = 0.4178$, $p = 0.0039$), while a positive but weak correlation of ΔIGF-1/IGFBP-3 molar ratio with ΔHT-SDS was suggested with marginal significance ($p = 0.0576$). No significant correlation was observed in the LD group.

Overweight and obesity

Three children (5.1 %) in the LD group and one (1.7 %) in the HD group were overweight at baseline, whereas two children (3.4 %) in the LD group were obese. No difference in the rate of overweight or obesity was observed between the two groups ($p = 0.081$). At week 104, the majority of children had normal weight; only two (one from each treatment group) were considered overweight and none were obese. There was no difference in the rate of overweight or obesity between the two groups (2.0 % vs. 2.0 %; $p = 0.989$).

Adverse events, glucose metabolism, and thyroid function

Treatment-emergent AEs (TEAEs) are listed in ▶ **Table 3**. There were 49 (83.1 %) and 52 (88.1 %) patients in the LD and HD groups, respectively, who experienced at least one TEAE ($p = 0.432$). Most of the TEAEs were mild or moderate in severity. A total of 12 patients experienced 15 serious AEs (SAEs), with no difference of incidence rates between the LD group (n = 5, 8.5 %) and HD group (n = 7, 11.9 %; $p = 0.542$). Hip dislocation; cryptorchidism surgery; anaphylactoid purpura; bilateral congenital cataract; hand, foot, and mouth disease; circumcision; viral encephalitis; hydrocele surgery; pneumonia; and bronchopneumonia were reported in 10 patients (n = 1 for each condition). For the remaining two patients, one experienced tonsillitis and adenoid hypertrophy, while the other had bronchitis recurring three times; both were in the HD group. Hip dislocation led to study discontinuation in one patient in the HD

▶ **Table 1** Patient demographics and baseline chracteristiscs of the FAS.

	0.23 mg/kg/ week (n = 59)	0.46 mg/kg/ week (n = 58)	p-Value
Chronological age, years	4.77 ± 1.16	4.66 ± 1.27	0.626
Gender			
Male, n (%)	36 (61.02)	35 (60.34)	0.941
Female, n (%)	23 (38.98)	23 (39.66)	
Ethnicity			
Han (%)	58 (98.31)	57 (92.28)	1.000
Others (%)	1 (1.69)	1 (1.72)	
Birth length, cm	46.1 ± 3.5	46.5 ± 2.8	0.593
Birth length, SDS[a]	−0.08 ± 0.07	−0.07 ± 0.05	0.577
Birth weight, kg	2.20 ± 0.31	2.30 ± 0.29	0.087
Birth weight, SDS[a]	−2.29 ± 0.09	−2.27 ± 0.08	0.086
Head circumference at birth, cm	29.4 ± 3.1	30.5 ± 2.9	0.168
Parental height, cm			
Father	168.3 ± 6.7	167.9 ± 6.1	0.749
Mother	156.0 ± 6.3	155.3 ± 5.3	0.527
Parental height, SDS[b]			
Father	−0.02 ± 0.04	−0.03 ± 0.03	0.749
Mother	−0.03 ± 0.04	−0.03 ± 0.03	0.527
Genetic target height, cm	163.6 ± 7.7	163.1 ± 7.2	0.692
Pituitary gland MRI, n (%)			
Normal	46 (83.64)	47 (82.46)	0.868
Abnormal	9 (16.36)	10 (17.54)	
HT-SDS	−2.77 ± 1.14	−2.89 ± 1.11	0.580
Height, cm	95.6 ± 7.9	94.2 ± 9.8	0.410
BA, years	3.04 ± 1.04	2.91 ± 1.10	0.497
IGF-1, ng/ml	95.25 ± 43.27	78.90 ± 50.42	0.064
IGF-1/IGFBP-3	0.10 ± 0.03	0.09 ± 0.04	0.043

BA: Bone age; FAS: Full analysis set; HT-SDS: Height SD score; IGFBP-3: IGF binding protein-3; MRI: Magnetic resonance imaging.; [a] Calculated using data of newborns from the 2005 physical development survey of children aged 0–18 years in nine cities in China as reference.; [b] Calculated using data of 18-year-olds from the 2005 physical development survey of children aged 0–18 years in nine cities in China as reference.

group. Nevertheless, all these SAEs were unrelated to study treatment and were resolved without sequelae. Treatment-related AEs (TRAEs) occurred in 14 (23.7 %) and 20 (33.9 %) patients in the LD and HD groups, respectively (p = 0.223). They were mainly injection-site reactions, abnormal clinical laboratory findings, and non-specific symptoms such as allergic dermatitis, arthralgia, and limb pain. The majority of these TRAEs were transient, self-limiting, and related to accelerated growth as a result of rhGH treatment.

FPG, 2-h post-prandial blood glucose level (2hPBG), and FINS levels increased slightly after 12 months, but were within the normal reference range throughout 24 months. Mean HbA1c values were constantly around 5.4 % at treatment initiation and throughout the course of treatment. Serum TT4 levels exhibited a downward trend for 24 months while TT3 and TSH levels remained stable; all these three parameters were well within the normal range. No statistically significant difference for glycemic and thyroid function indicators was found between the LD and HD groups (data not shown).

Antihuman GH antibodies

Antihuman GH antibodies were detected in two patients in the LD group and five in the HD group at weeks 26, 52, and 78, but were negative at week 104.

Effect of long-term GH treatment

HT-SDS, ΔHT-SDS, AH, and BMI

Children born SGA continued to benefit from GH treatment beyond 104 weeks. Mean HT-SDS at the start of the extended follow-up was −1.38, increased annually to −0.98 on the third year and reached −0.91 in 23 patients who were treated for ≥ 5 years (▶ **Fig. 3a**). The ΔHT-SDS also increased with prolongation of treatment, remaining above + 2 from the third year (▶ **Fig. 3b**). Most children (≥ 80 %) had BMI within the normal range during the long-term follow-up.

Among the 30 patients who reached AH, 12 were males and 18 were females. Mean AH-SDS was −0.81 ± 1.68 and −0.82 ± 1.05 for male and female patients (p = 0.9837), respectively (▶ **Fig. 4**), which was within the normal population range (between −2 and + 2 SDS). A total of 23 patients [76.7 %; male: 8 (66.7 %), female: 15 (83.3 %), **Fig. 1aS** and **1bS**] achieved a height gain of ≥ 1 SDS compared with baseline, indicating that most children can improve their AH through long-term rhGH therapy.

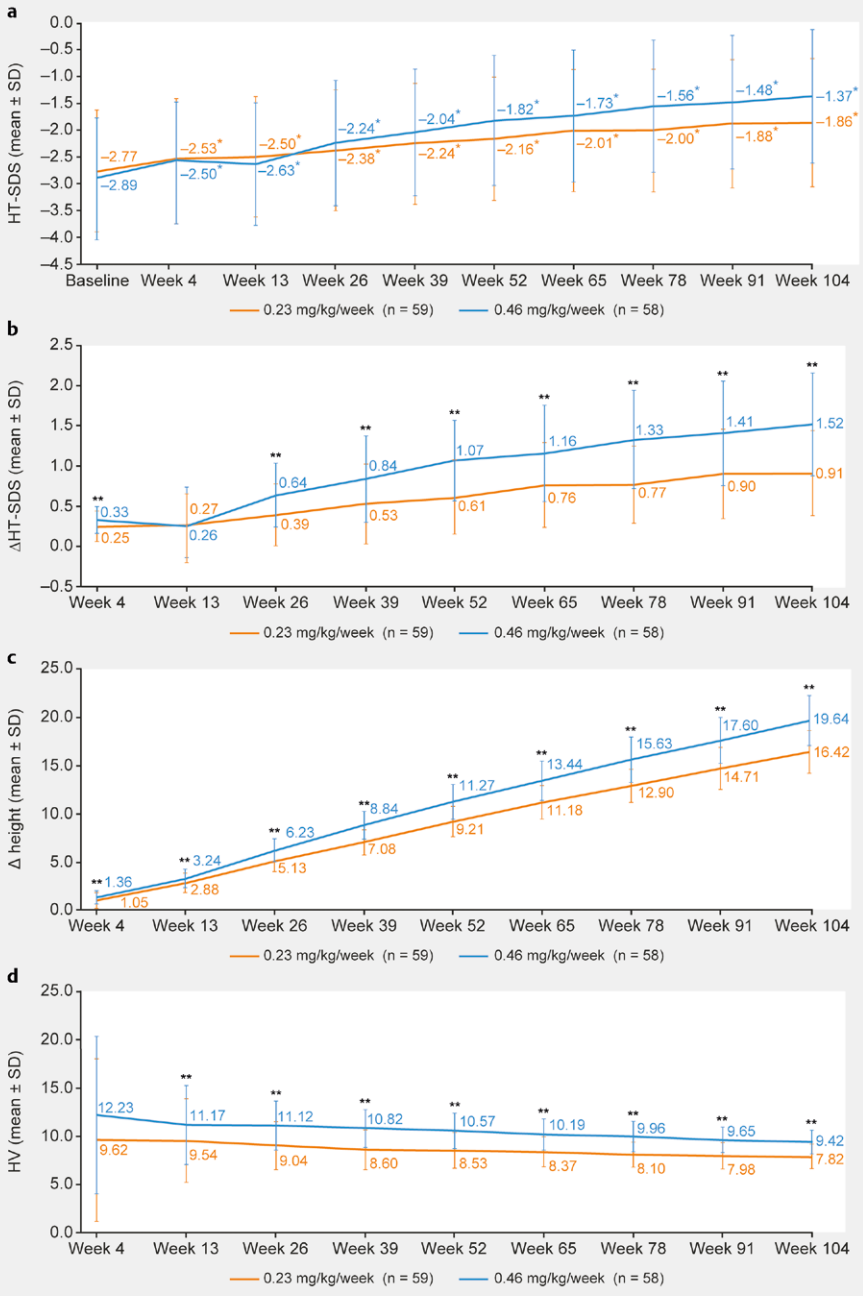
Trajectories of the BMI SDS of the patients who reached AH are shown in **Fig. 2S**. For both genders, BMI SDS remained stable throughout the follow-up with mean values within ± 1, indicating that long-term rhGH treatment may not considerably impact weight gain.

Glucose metabolism and thyroid function

FPG, 2hPBG, and HbA1c levels were stable overall and well within the normal reference range throughout extended follow-up (**Fig. 3aS**–**3cS**). Although there was an increment in FINS, results at each evaluable time point were within the normal reference range (5–20 μIU/ml; **Fig. 3dS**). TT3 (**Fig. 4aS**), TT4 (**Fig. 4bS**), and TSH (**Fig. 4cS**) levels were all in the normal range though a downward trend with fluctuations was observed. No hypothyroidism or diabetes were reported.

Discussion

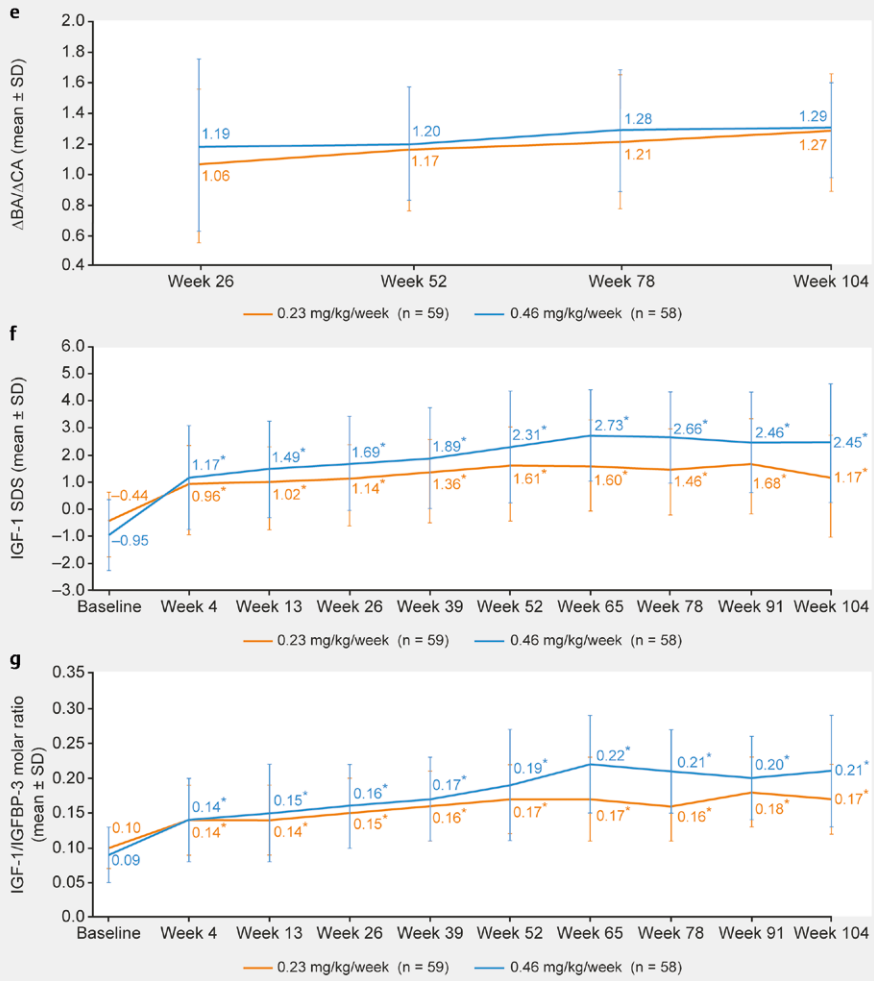
Although the clinical benefits of long-term continuous GH therapy for children born SGA have been well demonstrated in Western countries and Japan [7, 9, 12], there are insufficient data in the Chinese population. Our multicenter study not only provided an in-depth understanding of the effect of rhGH treatment on growth parameters, glucose metabolism, and thyroid function under two



▶ **Fig. 2** **a**: HT-SDS, **b**: ΔHT-SDS, **c:** Δ height, **d**: HV, **e**: ΔBA/ΔCA, **f**: IGF-1 SDS, and **g**: IGF-1/IGFBP-3 molar ratio of the FAS at each evaluable time point. Δ: Change in; BA: Bone age; CA: Chronological age; FAS: Full analysis set; HT: Height; HT-SDS: Height SD score; HV: Height velocity; IGF-1 SDS: IGF 1 SD score; IGFBP-3: IGF binding protein-3; SDS: SD score. * Within-group $p<0.05$; ** Intergroup $p<0.05$.

different doses over a 2-year period, but also on the long-term effectiveness and safety of rhGH therapy in the extended treatment and follow-up of up to 10 years in short stature Chinese children born SGA.

Our study showed an upward trend in HT-SDS during the first 2 years of treatment; at week 104, HT-SDS was above −2 SDS (LD: −1.86 ± 1.18, HD: −1.37 ± 1.24), suggesting that catch-up growth was achieved with both GH doses. A similar trend was observed with ΔHT-SDS, showing increments of 0.91 ± 0.53 and 1.52 ± 0.64 from baseline to week 104 in the LD and HD groups, respectively. In a Japanese study of SGA children who initiated treatment at a similar CA as our study population, Yokoya et al. reported that ΔHT-SDS increased by 0.84 ± 0.42 in the 0.23 mg/kg/week group and by 1.50 ± 0.44 in the 0.47 mg/kg/week group at 2 years [8]. Sas et al. showed HT-SDS of about −1.7 and −1.2 at 24 months in 79 SGA children who were treated continuously with 3 IU/m^2/day or 6 IU/m^2/day GH, respectively [10]. A mathematical model – created based on a meta-analysis of 10 trials totaling 510 patients to describe the



▶ **Fig. 2** Continued.

dose–response relationship of rhGH in children born SGA – yielded an additional gain of 0.48 ± 0.42 HT-SDS in those who received GH treatment at 0.067 mg/kg/day (approximately 0.47 mg/kg/week) compared with 0.033 mg/kg/day (approximately 0.23 mg/kg/week) after 2 years of treatment [22]. Our findings conformed to the dose–response relationship favoring the HD group in terms of the growth parameters (ΔHT-SDS, Δ height, and HV), but those who received the lower dose of rhGH also showed meaningful therapeutic improvement.

Serum concentration of IGF-1 is a widely used indicator to monitor rhGH treatment [23]. Our observations were consistent with other reports that IGF-1 SDS increased most significantly during the initial 4 weeks of GH treatment, and a dose–response relationship was also observed with higher levels of serum IGF-1 SDS found in the 0.067 mg/kg/day group [7, 8]. Associations between IGF-1 and treatment response to rhGH have been investigated in several studies on SGA children: Kappelgaard et al. found a positive correlation between ΔHT-SDS and ΔIGF-1 SDS over 260 weeks of treatment in doses of 0.033 mg/kg/day ($r = 0.715$, $p < 0.0001$) and 0.067 mg/kg/day ($r = 0.579$, $p = 0.0010$), respectively [9]. Compared with poor responders, those with adequate response during the first year of therapy (defined at a cut-off value of 0.3 for ΔHT-SDS) had higher ΔIGF-1 SDS (3.58 ± 1.49 vs. 2.37 ± 1.66 SDS, $p < 0.05$) [24]. Recent data from Korean SGA children indicated ΔIGF-1 SDS at 2 years as the only influencing factor (correlation analysis: $r = 0.425$, $p = 0.012$; multiple regression analysis: $\beta = 0.047$, $p = 0.041$) associated with treatment response (ΔHT-SDS) [25]. Our analysis was also in line with the above in that ΔIGF-1 SDS was positively and significantly correlated with ΔHT-SDS at 2 years; however, this association was only revealed in the HD group.

Whether to recommend IGF-1/IGFBP-3 molar ratio as a tool for monitoring rhGH therapy is controversial: Wegmann et al. found no correlation of ΔIGF-1/IGFBP-3 molar ratio with either change in bioactive IGF-1 or change in height, which challenges the previous viewpoint that IGF-1/IGFBP-3 molar ratio reflects the availability of free IGF-1 [26]. Ballerini et al. found a higher IGF-1/IGFBP-3 molar ratio SDS (0.64 ± 1.04 vs. −0.31 ± 0.43; $p < 0.015$) and ΔIGF-1/IGFBP-3 molar ratio SDS (1.06 ± 0.86 vs. 0.24 ± 0.57 SDS; $p < 0.05$) in children with SGA who achieved a ΔHT-SDS ≥ 0.3 than those < 0.3 in the first year of treatment [24]. Despite that, they considered IGF-1/IGFBP-3

▶ **Table 2** Correlation analyses of IGF-1 SDS, IGF-1/IGFBP-3 molar ratio, and their corresponding changes from baseline with treatment response (ΔHT-SDS).

Variable	LD group		HD group	
	r-Value	p-Value	r-Value	p-Value
First year				
ΔIGF-1 SDS	0.0886	0.5323	0.1791	0.2040
ΔIGF1/IGFBP-3 molar ratio	0.0944	0.5055	0.0590	0.6780
IGF-1 SDS	0.0574	0.6860	0.0337	0.8106
IGF1/IGFBP-3 molar ratio	0.1825	0.1953	−0.0388	0.7827
Second year				
ΔIGF-1 SDS	0.0757	0.6254	0.4178	0.0039
ΔIGF-1/IGFBP-3 molar ratio	0.2308	0.1317	0.2820	0.0576
IGF-1 SDS	−0.0711	0.6466	0.2525	0.0905
IGF-1/IGFBP-3 molar ratio	0.2692	0.0772	0.1889	0.2088

Δ: Change in; HD: High dose; HT-SDS: Height SD score; IGFBP-3: IGF binding protein-3; LD: Low dose; SDS: SD score.

▶ **Table 3** Treatment-emergent adverse events of the SS.

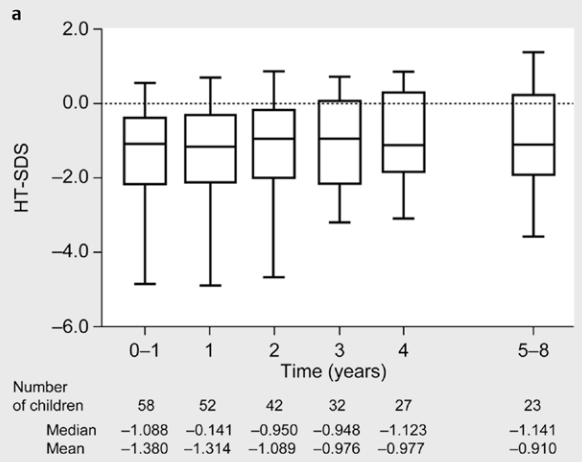
	0.23 mg/kg/week (n = 59) n (%)	0.46 mg/kg/week (n = 59) n (%)	Total (n = 118) n (%)
TEAEs	49 (83.1)	52 (88.1)	101 (85.6)
TRAEs	14 (23.7)	20 (33.9)	34 (28.8)
SAEs	5 (8.5)	7 (11.9)	12 (10.2)
Treatment suspension due to TEAEs	1 (1.7)	1 (1.7)	2 (1.7)
TEAEs occurring in ≥ 5 % of subjects in any group			
Upper respiratory tract infection	32 (54.2)	31 (52.5)	63 (53.4)
Fever	10 (17.0)	11 (18.6)	21 (17.8)
Cough	7 (11.9)	11 (18.6)	18 (15.3)
Elevated blood insulin	8 (13.6)	10 (17.0)	18 (15.3)
Rhinitis	6 (10.2)	7 (11.9)	13 (11.0)
Rash	1 (1.7)	6 (10.2)	7 (5.9)
Respiratory infection	5 (8.5)	2 (3.4)	7 (5.9)
Vomit	4 (6.8)	3 (5.1)	7 (5.9)
Tonsilitis	2 (3.4)	4 (6.8)	6 (5.1)
Abdominal pain	3 (5.1)	3 (5.1)	6 (5.1)
Bronchitis	1 (1.7)	4 (6.8)	5 (4.2)
Elevated blood glucose	4 (6.8)	1 (1.7)	5 (4.2)
Head injury	0 (0.0)	5 (8.5)	5 (4.2)
Pneumonia	3 (5.1)	0 (0.0)	4 (3.4)
Sneezing	0 (0.0)	3 (5.1)	3 (2.5)
Indigestion	3 (5.1)	0 (0.0)	3 (2.5)

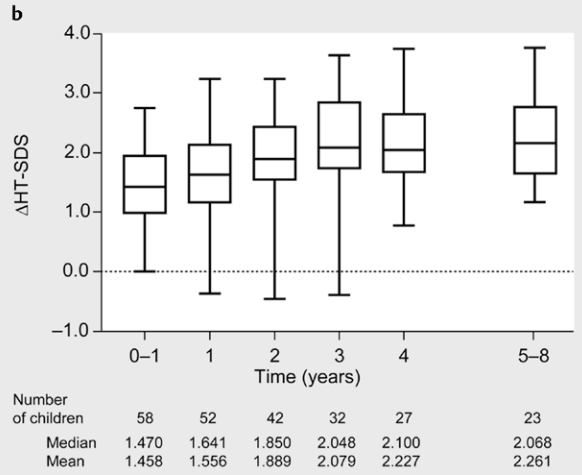
SAE: Serious adverse event; SS: Safety set; TEAE: Treatment-emergent adverse event; TRAE: Treatment-related adverse event.

molar ratio a less informative tool than IGF-1 due to the lack of solid reference intervals and potential bias from insulin actions [24]. Perspectives of the Growth Hormone Research Society (GRS) showed no compelling evidence to support the use of IGF-1/IGFBP-3 molar ratio in monitoring rhGH treatment [27]. On the contrary, IGF-1/IGFBP-3 molar ratio was perceived by other researchers to give extra guidance to the optimization of rhGH dosing, as high levels of IGF-1 implicate elevated risks of cancer, whereas high concentrations of IGFBP-3 were protective against cancer but associated with cardiovascular and metabolic disorders [22]. IGF-1/IGFBP-3 molar ratio increased significantly from baseline at all assessment points throughout 2 years in our patients, with greater increments in the 0.46 mg/kg/week group than the 0.23 mg/kg/week group. We also observed a weakly positive correlation of ΔIGF1/IGFBP3 molar ratio with ΔHT-SDS at 2 years in the HD group (r = 0.2820, p = 0.0576). Our findings conform to the previous reports that treatment with rhGH led to elevated IGF-1/IGFBP-3 molar ratio, with a higher value implicating more pronounced height gain [7, 24].

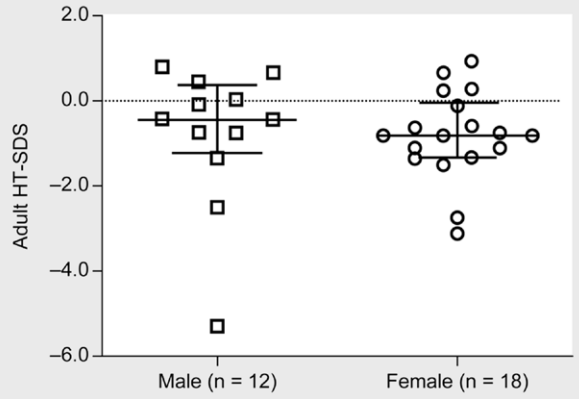
Supraphysiological level of serum IGF-1 has been associated with an increased risk of some cancers in later life, thus an IGF-1 concentration below + 2 SDS is recommended for GH therapies [23]. In our study, 62.3 % and 52.0 % of patients in the HD group had IGF-1 SDS > + 2 at weeks 52 and 104, respectively. Ballerini et al. reported in their retrospective study that 52 % and 54 % of children born SGA had IGF-1 above + 2 SDS after 1- and 2 years of rhGH therapy, respectively [24]. In a recent study, as many as 68 % of SGA children treated with 0.067 mg/kg/day rhGH had an IGF-1 concentration > + 2 SDS, yet only 15 % had their bioactive IGF-1 level slightly above the normal reference range [26]. Non-GHD conditions such as SGA may sometimes be accompanied with IGF-1 insensitivity, therefore, IGF-1 > + 2 SDS is needed to maintain effective growth [27]. This is supported by our observation of a positive correlation of ΔIGF-1 SDS with height response in the HD group. Even though high doses of rhGH therapy may lead to an elevated IGF-1 level above + 2 SDS, bioactive IGF-1 in the free form can still be kept in the acceptable range [26].

The Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) study, comprising 24 232 patients treated with rhGH during childhood with over 400 000 patient-years of follow-up, indicated no association between mortality and mean daily or cumulative doses of rhGH [28]. Cancer risk was not associated with duration or cumulative dose of rhGH treatment, yet cancer mortality risk in relation to GH dose was observed in patients with previous cancer, and incidence of bone and bladder cancers also increased for those without previous cancer [29]. One possible explanation is that the presence of genetic syndromes has an intrinsic risk of morbidity and mortality that may be triggered by GH





▶ **Fig. 3** Long-term **a**: HT-SDS and **b**: ΔHT-SDS data from the follow-up phase. Δ: Change in; HT-SDS: Height SD score.



▶ **Fig. 4** Final adult height attained at the end of follow-up. HT-SDS: Height SD score.

therapy [30]. As revealed by genetic screening, syndromic disorders associated with an increased risk of malignancies can also relate to certain SGA phenotypes, therefore, long-term surveillance is needed in all patients treated with rhGH and dosing regimens should be tailored for those with genetic predispositions to optimize the overall benefit-to-risk profile [30].

Sas et al. reported that annualized ΔBA/ΔCA during the 5-year treatment with GH was significantly higher than 1 but no differences were found between those who received 3 IU/m^2/day and 6 IU/m^2/day [10]. We observed, in a consistent manner, that treatment at a higher dose of 0.46 mg/kg/week would not lead to excessive bone maturation when compared with the lower dose of 0.23 mg/kg/week. However, our 2-year results revealed a ΔBA/ΔCA value closer to 1 than that reported by Sas et al., indicating that rhGH treatment did not exacerbate the rate of BA advancement in relation to age progression. Of note, a spontaneous and rapid acceleration of BA was found in many untreated SGA children over 3 years before the onset of puberty [31].

The long-term effect of GH treatment has been investigated in a number of studies for children born SGA. Tanaka et al. reported mean HT-SDS of –1.78 in the 33 µg/kg/day group and –0.82 in the 67 µg/kg/day group after 5 years of treatment, corresponding to the mean ΔHT-SDS of 1.22 and 2.01, respectively [7]. Consistent findings were also observed in other studies with HT-SDS above –2 at the end of 5-year treatment and it remained higher in the HD than the LD group [10, 12]. Results from an ongoing, international, non-interventional study showed a steady increment of HT-SDS from below –3 at baseline to about –1.5 over 5 years of rhGH treatment, leading to an improvement in HT-SDS of 1.85 among 270 children born SGA [32]. Another open-label, longitudinal study reported an increment of HT-SDS from –3.02 ± 0.65 at baseline to –1.23 ± 0.91 after 5 years of GH treatment ($p < 0.001$), achieving a ΔHT-SDS of 1.80 ± 0.72 [33]. Continuous improvement of HT-SDS after 2 years was also observed in our present study, with patients who were treated for a total of 7 years or more obtaining a gain in HT-SDS of + 2.26. As with Horikawa et al., of which only a small number of patients remained in the cohort after 5 years [33], our trends need to be interpreted with caution since extended follow-up data for ≥ 5 years were based on 23 children.

Very few studies investigated the effect of rhGH on AH in different genders. Of the 32 patients naïve to rhGH treatment who achieved near AH through treatment, Horikawa et al. reported a mean HT-SDS of –1.77 ± 0.75 in 7 boys and –2.10 ± 0.78 in 25 girls [33]. In contrast, mean AH SDS in both genders was above –2 in our patient population with no difference found between males and females. While our study showed that long-term GH treatment can normalize AH in most children born SGA, around 20 % failed to improve so this implies the presence of individual variability in treatment response. It is worth noting that polymorphisms in the *IGF-1* gene and the d3-Growth Hormone Receptor gene may explain the variability of responsiveness to GH treatment in children born SGA [34, 35]. Future studies are warranted to clarify the relationship between responses to rhGH treatment and genetic polymorphisms in SGA to better improve the AH of these children.

Anti-insulin effects associated with long-term administration of rhGH can be a concern for glucose metabolism since children with SGA are prone to insulin resistance at baseline [36]. In our present study, FPG, 2hPBG, and HbA1c levels remained well within the normal range throughout the entire treatment period with no significant difference found between the two dose groups; fasting insulin levels were also similar and, despite increment in the long-term follow-up, they were still within the normal reference range. Our observations on glucose tolerance and insulin sensitivity were consistent with the trends observed in other long-term studies [6, 12, 33]. Elevated fasting insulin levels could be explained by compensatory hyperinsulinemia that countered the GH-mediated increase in insulin resistance to maintain normal glucose regulation during treatment [37]; insulin levels returned to normal after treatment cessation [12]. No health implications arising from elevated fasting insulin levels were found by Horikawa et al. in children born SGA who received GH treatment for up to 9 years [33]. The authors attributed part of the change in insulin levels during long-term GH treatment to the natural changes in insulin metabolism when children transitioned to puberty, as more insulin is secreted to compensate for the lower insulin sensitivity that occurs during puberty.

Change in thyroid function during rhGH therapy has long been reported for GHD children, with decreases in thyroxine level frequently observed [13]. However, few studies investigated this effect in children born SGA. de Kort et al. showed that in 264 prepubertal children born SGA who received 24 months of GH treatment, mean FT4 decreased significantly during the first 6 months, but returned to the normal range thereafter; serum TSH levels and growth response to treatment were not affected [15]. A retrospective review of data from 25 short stature children born SGA reported higher serum FT4 at 12 and 24 months than at baseline, whereas serum TSH was significantly lower at 3 and 6 months; overall, in these children, thyroid function parameters were not altered by GH therapy [14]. Our results were consistent with the above findings that continuous rhGH therapy did not impact thyroid function at a dose of either 0.23 mg/kg/week or 0.46 mg/kg/week for 24 months. Additionally, we have shown that, despite a downward trend observed for thyroid hormones (TT3, TT4, TSH) beyond 24 months in the extended follow-up, they had little clinical significance and hence no safety issues regarding thyroid function were indicated with long-term treatment.

Our multicenter study not only provides an in-depth evaluation on the efficacy and safety of different doses of rhGH in short stature Chinese children born SGA, but also revealed the long-term effect of rhGH on growth parameters, glucose metabolism, and thyroid function in those who continued to receive treatment for a total of up to 12 years. To our knowledge, this is the first study that preliminarily assessed thyroid function change among SGA children administering rhGH for over 2 years. The limitation of this study, however, is the small number of patients with available data at ≥ 5 years, thus reducing the robustness of our long-term results. This has also been recognized in the long-term study by Horikawa et al. [33]. In addition, since the extended phase analysis was planned in a post-hoc manner, we were unable to calculate the mean dose of rhGH, as it was not mandatory to record this information. As such, the different rhGH dose used for each patient in the extended phase could potentially confound the study results and therefore, the long-term efficacy outcomes should be interpreted with caution. Nonetheless, our long-term outcomes are typical of rhGH treatment in real-world practice.

In conclusion, our study suggests that daily subcutaneous injections of rhGH effectively improved height in children born SGA without negative impact on weight, IGF-1/IGFBP-3 molar ratio, bone maturation, glucose metabolism, and thyroid function. Both 0.23 mg/kg/week and 0.46 mg/kg/week treatment achieved favorable growth response compared with baseline, though a clear dose–response relationship favoring the higher dose group was observed. Additional follow-up data of up to 10 years demonstrated that long-term, continuous rhGH treatment can improve AH in patients, with no difference of height gain between genders. There was no deterioration in thyroid function and glucose metabolism during long-term rhGH therapy.

Acknowledgements

The authors thank the patients who participated in this trial, and their families, as well as the investigators, study coordinators, study teams, and nurses. Medical writing assistance was provided by Lawrence Law, MPH, from Parexel and was funded by GeneScience Pharmaceuticals.

Funding Information

GeneScience Pharmaceuticals

Conflict of Interest

The authors declare that they have no conflict of interest.

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