

First Clinical Study on Long-Acting Growth Hormone Therapy in Children with Turner Syndrome



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ABSTRACT

Study on long-acting growth hormone (LAGH) therapy in Turner syndrome (TS) is a 2-year retrospective study including patients diagnosed with TS from 2018–2021. Patients were divided into four groups: Group 1 to 4 were low dose (0.1 mg/kg/w), high-dose (0.2 mg/kg/w) LAGH, daily GH (0.38 mg/kg/w), and untreated control. The efficacy and safety data were analyzed. Seventy-five TS cases with the age 7.9 ± 2.9 years and the bone age 6.8 ± 2.8 years were recruited. In year 1: The change of height standard deviation score (Δ HtSDS) and height velocity (HV) in Group 2 were comparable to Group 3, both two groups were higher than Group 1. Δ HtSDS and HV in all GH treatment group were higher than untreated group. IGF1 increased in all treatment groups, only 4 cases had IGF1 > 3 SD. In year 2: Δ HtSDS and HV in Group 2 and 3 were comparable. Five cases had IGF1 > 3 SD. Correlation analysis for LAGH efficacy at year 1 indicated that baseline variables correlated with Δ HtSDS include: GH dose, CA (chronological age), and bone age (BA). The HV was positively correlated with baseline GH dose, HtSDS, IGF-1 SDS and negatively correlated with baseline CA, BA, and BMI. No GH-related serious adverse effects were observed. The high-dose LAGH treatment in TS patients is effective and safe as daily GH for 2 years. The favorable prognosis factors include sufficient GH dose and early treatment. IGF1 monitoring and weight control are important.

‡ Xinying Gao and Jijia Chen contributed equally to this work.

Introduction

Turner syndrome (TS), also known as congenital ovarian hypoplasia syndrome, was first reported by Turner in 1938. TS is composed of complete or partial haplo groups of the X chromosome. The most common clinical feature is the short stature. Above 95% TS patients suffer from varying degrees of growth disorders [1, 2], and it is believed that its possible etiology and pathogenesis are related to a haploinsufficiency of SHOX gene (short stature homeobox containing gene) [3]. In 1996, the US Food and Drug Administration (FDA) approved growth hormone for the treatment of Turner syndrome (TS). To date, multiple clinical studies have confirmed that GH treatment could effectively improve the final height in TS patients [4–7].

At present, GH treatment is mostly administered through daily subcutaneous injections, and poor compliance remains in long-term applications. In recent years, the development and applications of LAGH have become a research hotspot worldwide; most of such studies are in phases 2 and 3 of the clinical trials [8–11]. The publication of Miller et al. [12] in 2020 compared studies published between January 2000 and June 2019, and showed that all subjects belonged to growth hormone deficiency (GHD). Seven RCT studies were completed, and all concluded a non-inferiority compared to daily GH, but it is still necessary to observe the long-term compliance, safety, and effectiveness. Additionally, there had not been any clinical studies treating TS with LAGH prior to this study.

IGF1 is recognized as an important biomarker for monitoring the efficacy and safety. TS patients do not lack growth hormones, and usually require more than their physiological requirements to promote growing by producing high IGF1. Both IGF1 and IGFBP-3 have been reported to be expressed in tumor tissue, and plays an important role in regulating cell growth, apoptosis and tumor evolution [13]. Although there is no clear evidence linking rhGH to tumors [14–16], there is a need to monitor the safety of IGF1 in GH treatment based on the genetic background of TS children and reports of rare tumor genesis [17]. International guidelines on TS treatment recommend that IGF1 SDS should be maintained between 1 and 2 during rhGH treatment. When IGF1 SDS rises higher than 3, it is recommended to reduce the GH doses to ensure safety of the treatment [18]. However, titration of IGF1 was used in a study to treat TS patients, with a mean treatment duration of 6.7 years and a final height increase of only 3.2 cm [19].

Our study is the first to analyze the efficacy and safety of LAGH treatment for TS and discuss the IGF1 levels as part of the efficacy evaluation to provide basis and references for clinical treatments.

Patients and Methods

Patients

Our data were based on a cohort study conducted at Beijing Children's Hospital in 2018, which has been registered and approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University (No. 2018–178), and are in accordance with the Declaration of Helsinki. The parents or guardians of the pediatric patients provided Informed consent prior to GH treatment. The primary aim was to evaluate the efficacy and safety of recombinant

human growth hormone therapy in Chinese children with short stature.

In our study, pre-pubertal patients diagnosed with TS were included in our analysis. Clinical diagnoses were based on the judgment of the treating physician. Pre-puberty was defined as stage Tanner 1 for the breast and/or having no secondary sex characteristics.

Study design

All patients enrolled were divided into four groups according to the initial treatment: Group 1 was treated with low-dose LAGH (0.1 mg/kg/w); Group 2 was treated with high-dose LAGH (0.2 mg/kg/w); Group 3 was control group (daily GH group, 0.38 mg/kg/w); Group 4 was untreated control group (untreated or GH had not been administered for up to 3 months), and followed up for 2 years. But in the second year, GH dose of Group 1 (0.18 mg/kg/w) was increased to similar with Group 2 (0.2 mg/kg/w), number of Groups 3 was decreased only 7, 9 patients in Group 4 (n = 15) were beginning GH therapy and 4 patients failed to follow-up. So, study duration was divided into two phases, year 1 with all 4 groups and year 2 with just two, Group 2 and Group 3. The study flowchart for the analysis of the effects of GH therapy is shown in ► Fig. 1.

LAGH (Jintrolong®) is the irreversibly PEGylated LAGH formulation and was from Gene Science Pharmaceuticals, Changchun, China.

Methods

Assessments at baseline included chronological age, bone age, standing height, weight, parental height, HV, and GH dose. Predicted adult height = (father's height + mother's height)/2–6.5. HtSDS calculation was based on the 2005 percentile table of height and weight of children aged 0–18 in Chinese cities [20].

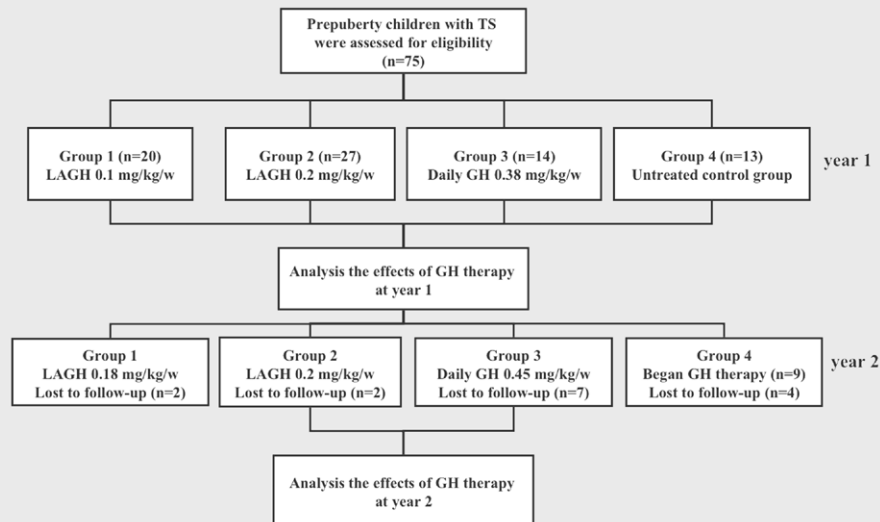
The following items were recorded during follow-ups: GH dose, height, weight, bone age, laboratory data included IGF1, glycated hemoglobin (HbA1c), cortisol, free thyroxine (T₄), thyroid-stimulating hormone (TSH), lipids, insulin, fasting blood glucose, 2-hour postprandial blood glucose, liver, and renal function. GH related side effects including intracranial hypertension, slippage of the femoral head, and tumor were analyses.

Serum IGF1 was determined by chemiluminescent immunoassay using an IMMULITE 2000 immunoassay system (Siemens Medical Diagnostics, Germany). IGF1 SDS was calculated according to normal reference values for Chinese children.

BA was assessed by the clinician using an X-ray image, according to the G-P method [21].

Statistical analysis

Data are presented as mean ± SD and percentages. Comparison of data between groups was performed using *t*-test or one-way analysis of variance (ANOVA). Post hoc analysis was performed with the Bonferroni's adjustment. Chi-square test/Fisher's exact test was used to compare the count data. Paired *t*-test was used for comparing differences between the baseline and treatment. Multivariate correlation analysis was conducted on the influencing factors of ΔHtSDS, HV during the LAGH treatment, and of which the results showed that *p* < 0.05 was statistically significant. SPSS version 22.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Graphs



► Fig. 1 The study flowchart.

were plotted using GraphPad Prism version 8.2 (San Diego, CA, USA).

Results

Baseline characteristics

Seventy-five prepubertal TS children were enrolled. The mean age was 7.9 ± 2.9 years, and the mean bone age was 6.8 ± 2.8 years. Baseline characteristics are shown in ► Table 1. The karyotypes of the 75 patients were 45, X0 ($n = 16$, 21%); mosaic karyotype ($n = 11$, 15%); chromosome structural abnormality ($n = 47$, 63%), and 1 case (1%) of 45, X0/46XY. The origin of the X chromosome: there were a total of 15 cases of 45, X0; the parental X chromosome origin of 12 of them was tested: 8 patients (67%) had maternal X chromosomes and 4 (33%) had paternal X chromosomes. The four groups were well balanced in terms of demographics and clinical characteristics ($p > 0.05$, ► Table 1). However, BMI showed differences between groups, ($p = 0.03$, ► Table 1), but the post hoc analysis identified no significant differences between these groups. The baseline IGF1SDS results of the four groups were -1.10 , -1.10 , -0.72 , -1.15 , respectively. There was no statistical difference between groups ($p = 0.448$).

The efficacy

Year 1

The mean HV of each Group (Group 1 to 4) was 6.7 cm/year, 8.4 cm/year, 7.7 cm/year, and 4.7 cm/year, respectively, and there was significant difference among 4 groups, ($p < 0.0001$). The treatment groups increased significantly from baseline ($p < 0.0001$) for all (► Table 2, ► Fig 2a) and Group 4 was lower than treatment group, there was no difference in the untreated group (Group 4), (► Table 1S). HtSDS increased from baseline between treatment groups, p -values for Groups 1, 2 and 3 were 0.003, < 0.0001 and 0.005 respectively, and Group 4 showed no difference, p value was 0.436 (► Table 2, ► Fig 2b). Com-

paring the change from baseline (Δ HtSDS) among groups as follows: there was significant difference between groups, ($p = 0.0002$) (► Table 2). Group 2 and Group 3 had higher Δ HtSDS than Group 4, and there was no difference between Group 1 and 4, Group 2 and 3 had higher Δ HtSDS than Group 1, while there was no difference between Groups 2 and 3 ($p > 0.99$) (► Table 1S, ► Fig 2c), which indicated that the effect of high-dose LAGH therapy (group 2) was similar compare to that of daily GH, and better than low-dose LAGH.

The trend of mean IGF1SDS levels between GH treatment groups at follow-up time point is shown in ► Fig. 3. Compared to the baseline, the levels of IGF1SDS are improved, and rapidly reached their peak between 6 to 9 months among treatment groups, and then reached a plateau. IGF1 levels in great majority of the patients treated with GH were in the normal range at follow-up time point (► Fig. 3). There were 1 patient (5%) in Group 1, 6 patients (21%) in group 2, 5 patients (33%) in Group 3 with IGF1 levels > 2 SD, and only 3 patients (7.1%) in Group 2. One patient (7.7%) in Group 3 had IGF1 levels > 3 SD.

The BA-CA between treatment groups (Group 1 to 3) at year 1 were -0.6 ± 1.0 ($n = 17$), -1.3 ± 1.0 ($n = 15$), -1.3 ± 1.1 ($n = 8$). Compared with the baseline -0.6 ± 1.0 ($n = 17$), -1.2 ± 1.0 ($n = 26$), -1.3 ± 1.1 ($n = 8$), -1.2 ± 1.1 ($n = 13$), there were no statistical differences in BA-CA between groups 1, 2, and 3. The p -values were 0.63, 0.11, and 0.13, respectively, and BA-CA did not accelerate.

Complementary additional analyses results

Multivariate correlation analysis in LAGH treatment at first year indicated that Δ HtSDS was positively correlated with baseline variables including baseline dose ($r = 0.33$, $p = 0.02$) and negatively correlated with baseline CA ($r = -0.32$, $p = 0.03$), and BA ($r = -0.54$, $p = 0.0002$). The HV was positively correlated with baseline HtSDS ($r = 0.33$, $p = 0.03$), IGF1SDS ($r = 0.38$, $p = 0.01$), and negatively correlated with baseline CA ($r = -0.67$, $p < 0.0001$), BA ($r = -0.71$, $p < 0.0001$), and BMI ($r = -0.36$, $p = 0.02$) (► Table 2S).

► **Table 1** Baseline Characteristics of the patients with TS.

	Group 1	Group 2	Group 3	Group 4	p
n	20	27	14	13	
GH dose	0.1	0.2	0.38	0	
Chronological age(year)	7.8±2.4	8.0±3.2	8.9±3.1	7.9±3.7	0.75
Karyotype, n (%)					0.70
45, X0	5 (25%)	7 (25%)	3 (20%)	1 (7.7%)	
X abnormal	13 (65%)	17 (61%)	7 (53%)	1 (76.9%)	
Mosaic	2 (10%)	3 (11%)	4 (27%)	2 (15.4%)	
Y chromosome material	0	1 (3%)	0	0	
Height (cm)	109.6±11.6	109.2±14.0	115.3±17.0	109.5±16.9	0.59
HtSDS	-3.23±0.52	-3.46±0.96	-3.27±0.89	-3.23±0.79	0.60
MPHSDS	0.39±0.57	0.51±0.93	0.29±0.69	0.85±0.91c	0.32
Weight (kg)	22.58±8.17	21.00±8.49	25.91±10.77	19.57±6.97	0.23
BMI (kg/m ²)	18.2±3.5	17.0±2.9	18.5±2.6	15.7±1.5	0.03
IGF-1 SDS	-1.10±1.24	-1.10±1.35	-0.72±0.80	-1.15±1.17	0.44
HV (cm/year)	3.2±1.1	3.9±1.5	3.4±0.9	3.9±1.4	0.18
BA (year) [#]	6.8±2.5	6.8±3.0	8.2±3.2	6.7±3.2	0.67
BA-CA (year) [#]	-0.6±1.0	-1.3±1.0	-1.3±1.1	-1.2±1.1	0.19

CA: Chronological age; BA: Bone age; HV: Height velocity; BMI: Body mass index; MPH: Mid-parental height; SDS: Standard deviation score. [#] The numbers of each group with bone age: Group 1 (n=18), Group 2 (n=26), Group 3 (n=8), Group 4 (n=13).

► **Table 2** Comparison of HtSDS, ΔHtSDS, and HV between groups in TS at year 1.

	Group 1	Group 2	Group 3	Group 4	p (ANOVA)
n	20	27	14	13	
HV	6.7±1.8	8.4±1.9	7.7±2.4	4.7±1.8	<0.0001
HtSDS at baseline	-3.23±0.52	-3.46±0.96	-3.27±0.89	-3.23±0.79	–
HtSDS at year 1	-2.86±0.62	-2.91±1.22	-2.69±0.76	-3.33±0.87	–
ΔHtSDS	0.31±0.42	0.56±0.43	0.68±0.69	0.12±0.44	0.0002

HV: Height velocity; ΔHtSDS: Change in HtSDS from baseline.

Year 2

Year 2 with just two groups, Group 2 (n=25) and Group 3 (n=7), GH dose of Group 3 (0.45 mg/kg/w) was slightly increased than year 1. The baseline HV of Group 2 was 3.3±1.5, significant increase to 6.3±2.1 at year 2 (p=0.0001), and Group 3 was -3.46±0.96, increasing to 6.6±1.2 (p<0.0001). The baseline HtSDS of Group 2 was -3.27±0.89, increasing to -2.84±1.18 (p=0.03), and Group 3 was -3.4±0.9, increasing to -2.68±1.17 (p=0.048), ΔHtSDS at year 2 between group 2 and 3 were similar (0.88±0.74 vs. 0.89±0.76, p=0.97). The effect of high-dose LAGH therapy was similar compared to that of daily rhGH.

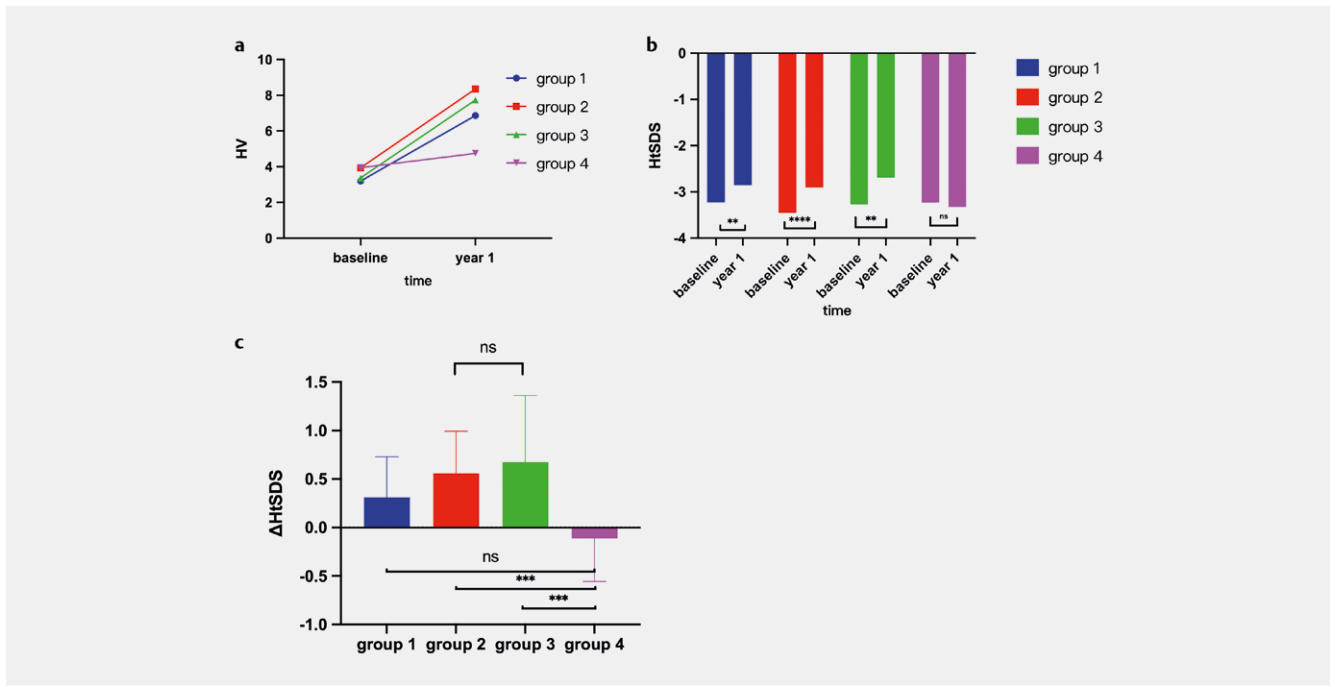
In the second year, the mean IGF1 level of 2 groups were 0.9±0.2, 1.9±1.0, p=0.1. Four patients (16%) in Group 2 and 1

patient (14.2%) in Group 3 had IGF1 levels >3 SD; the percentage of the 2 groups had no difference.

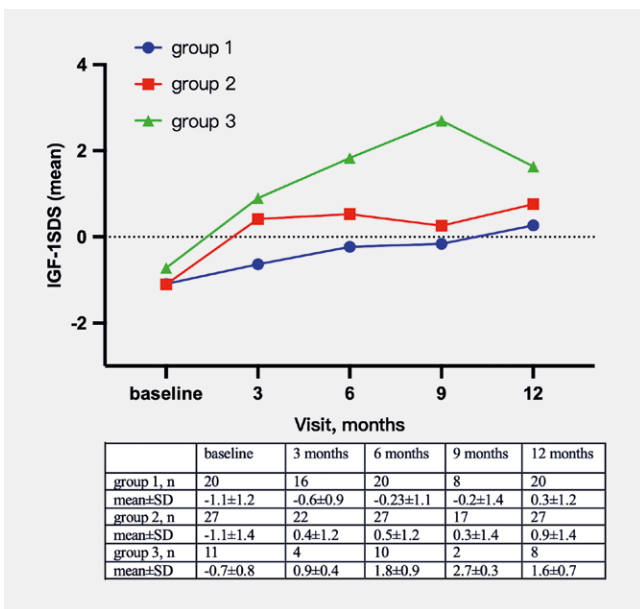
The BA-CA at year 2 between Group 2 (-1.3±1.2, n=11) and Group 3 (-1±0.3, n=4) was comparable (p=0.78). Bone age delay in relation to the chronological age in both two groups.

Safety

Over the 2 years' treatment, no serious adverse events occurred, only 4 mild to moderate drug-related adverse events were reported. One patient from low-dose LAGH group had elevated TSH level, but free T₄ was within the normal range, and TSH returned to normal at follow-up time after thyroxine supplementation. One patient from high-dose LAGH group had injection site nodules, and nodules disappeared at follow-up time when the patient changed



► **Fig. 2** a: Comparison of height velocity (HV) among groups at baseline and year 1; b: Comparison of height standard deviation score (HtSDS) among groups at baseline and year 1; c: Comparison of change in height standard deviation score from baseline to year 1 (Δ HtSDS) among groups.



► **Fig. 3** The trend of mean insulin-like growth factor 1 standard deviation score (IGF1SDS) at visit time between GH treatment groups (Groups 1 to 3).

the injection site. The other two events occurred in daily rhGH group, two patients had hyperinsulinemia, and one of them was considered to have impaired glucose tolerance, which required take metformin, no type 2 diabetes mellitus occurred, there was no injection site acting, including erythema, lipoatrophy and notable post-injection pain occurred. No serious adverse events including

intracranial hypertension, slipped capital femoral epiphysis, scoliosis, or tumor, etc. side effects developed in both groups. The patient received GH treatment had normal HbA1c, liver and kidney functions, and there were no adverse events led to the discontinuation of GH therapy.

Discussion

Our research is the first study of LAGH therapy in children with TS. Patients received injections of PEG rhGH weekly. Our first-year study demonstrated that high-dose LAGH can significantly improve HtSDS and HV of TS compared to low-dose LAGH, multiple variable analyses showed high dose positively correlated with better outcome. For the second year, the mean dose in the low-dose LAGH group was increased to 0.18 mg/kg/w to maintain HV more than 6 cm/year. The effect of high-dose LAGH was similar to that of the daily rhGH at a dose of 0.38 to 0.45 mg/kg/w through a 2-year period. Both two groups showed higher HV and Δ HtSDS comparing with low-dose group. Literature indicated that dose in first year is a major factor contributing to total response for TS [22], so our study emphasized that the highest safe dose in the first year is important for a better outcome, especially in girls with a poor adult height prognosis [23].

During GH treatment, IGF1 was measured for both safety and efficacy. In our study, IGF1 levels were monitored during the full treatment period. We discovered a rapid IGF1 increase, which reached its peak between 6 to 9 months among treatment groups, then maintained stable. Most of the IGF1 values were within the normal range, only 3 patients (7.1%) in Group 2 and 1 patient (7.7%) in Group 3 had got IGF1 levels > 3 SD at year 1. In the second

year, 4 patients (16%) in Group 2 and 1 patient (14.2%) in Group 3 had IGF1 levels > 3 SD. The IGF-1 level between the 2 groups were comparable, the prescribing physician did not decrease the GH dose, and IGF-1 levels after transient were elevated, decreased, or maintain stable at follow-up visits. Our study describes the common dosing patterns in clinical practice. Physician chosen to fix the dosage based on the weight and adjusted dosages according to HV. Compared with the IGF1 titration method, this approach is effective and relatively safe in short term study. Long-term follow-up is needed to confirm this conclusion, and if an IGF-I value is continued above + 3 SDS, GH dose should be decreased, but there is a problem concerned about to choose an appropriate detection method and IGF1 reference.

We also observed the safety of GH therapy. The common side effects are injection site acting, headache, and muscle or joint pain, serious side effects including benign intracranial hypertension, type 2 diabetes mellitus (T2DM), and slipped capital femoral epiphysis (SCFE) and tumors. LAGH related adverse events include edema injection-site lipoatrophy, etc. No serious side effects occurred in our study. Only 4 mild to moderate drug-related adverse events were reported. One patient from low-dose LAGH group had elevating TSH level, and normal free T₄ level, and TSH returned to normal at follow up time after thyroxine supplementation. TS is susceptible to immune diseases, including thyroid disease. So, whether or not beginning growth hormone therapy, it is important to measure (free) T₄ and TSH levels. No injection-site lipoatrophy was observed, but 1 patient from high-dose LAGH group had injection site nodules, when the patient changed the injection site the nodules disappeared. In the long-acting PEGylated rhGH phase III and phase IV randomized controlled trails, there is no injection-site lipoatrophy reported [24, 25], but some clinical study showed that at 13 weeks after GH treatment, injection-site lipoatrophy occurred, when the injection-site was changed and to avoid repeated injections on the same site, injection-site lipoatrophy recovered after 3–6 months. The other two events occurred in daily rhGH group, two patients had hyperinsulinemia, no type 2 diabetes mellitus occurred. Previous study indicated that incidence of diabetes mellitus and impaired glucose tolerance in children with GH treatment are higher than not treated [26]. But it is still controversial, some study suggested that GH treatment reduced abdominal adiposity and significantly improved glucose tolerance. In our study, HbA1c, liver, and kidney function, total cholesterol was within normal range among all treatment groups. There is no acceleration in BA.

The previous studies have shown that the efficacy of Turner syndrome is related to the dose of GH, age of treatment initiation, and duration of treatment. Younger age, longer treatment duration and higher initial GH dose, may result in relative better outcomes [27]. In our study, multivariate correlation analysis of LAGH treatment came to the similar conclusion, which was consistent with the relevant studies of daily rhGH. We also found that the therapeutic response in year 1 was positive correlated with baseline IGF1, HtSDS, and negative correlated with baseline BMI. Previous studies [28] also found that baseline weight is GH treatment response predictor (the lower baseline weight associated with the increase of height SD score), as well as the risk of metabolism in TS patients

are closely associated with weight gain, we then emphasized the importance of weight control.

Compared with previous studies, our study found several correlation factors affecting the efficacy of LAGH were as follows: in year 1, patients with younger age, younger bone age and higher IGF1SDS at baseline received a better effect, which was confirmed in the study of GHD and daily GH treatment of TS.

In actual clinical settings, clinicians generally adopt treatment plans based on the weight-based treatment regimens. Compared to IGF1 titration, it showed benefit of height gain. During the two-year treatment, IGF1 of most patients were within the normal range. Even if it occasionally exceeded 3SD, it could be reduced to normal level without reducing dose.

Strengths and Limitations

The strength of the study is the fairly large size of the study cohort and first-time evaluation efficacy of LAGH in TS. The limitations are the relatively short observation period and not obtaining the ultimate height of patients. We would further investigate the long-term efficacy and safety for LAGH treatment in the future.

Conclusion

Our research first assessed the efficacy and safety of LAGH treatment in Turner syndrome. Our study demonstrated that the effect of high-dose LAGH (0.2 mg/kg/w) was similar compared with daily rhGH (0.38 to 0.45 mg/kg/w) in TS treatment, concerning about practical questions, such as dose adjustment of GH, and IGF1 monitoring. Compared with IGF1 titration method, a fixed GH dose according to weight and adjust GH dose according to therapeutic response could effectively improve height gain. Sufficient GH dose, early diagnosis, and early treatment, high HtSDS and IGF1 level, lower BMI improved the first year outcomes. GH therapy does not accelerate epiphyseal healing. However, with continuous high dosage, monitoring IGF1 is important, especially in TS treatment, and the benefit of height gain should be weighed against the GH-related side effects, cost, and tolerance. There were no serious adverse effects. For TS, short-term LAGH treatment was effective and safe.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Notice

This article was changed according to the following Erratum on January 13th 2023.

Erratum

In the article mentioned above the shared first authorship was incorrectly declared. Correct is: Xinying Gao and Jiajia Chen contributed equally to this work.