Hormone and Metabolic Research

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

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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
Study on long-acting growth hormone (LAGH) therapy in Turner syndrome (TS). This 2-year retrospectively study included 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 in height standard deviation score (∆HtSDS) and height velocity (HV) in Group 2 were comparable to Group 3, both of the two groups were higher than Group 1. ∆HtSDS and HV in all GH treatment group higher than untreated group. IGF1 increased in all treatment groups, only 4 cases had IGF1> 3SD. In year 2: ∆HtSDS and HV in Group 2 and 3 were comparable. 5 cases had IGF1> 3SD. Correlation analysis for LAGH efficacy at year 1 indicated that baseline variables correlated with ∆HtSDS included: GH dose, CA (chronological age) and bone age (BA). The HV was positively correlated with baseline GH dose, HtSDS, IGF-1SDS 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, early treatment. IGF1 monitoring and weight control are important.

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Introduction

Turner syndrome (TS), also known as congenital ovarian hypoplasia syndrome, was first reported by Turner. H 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]. Miller et al’s [12] publication 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]. Though there lacks clear evidence showing a direct causal relation between rhGH and 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 IGF1SDS should be maintained between 1 and 2 during rhGH treatment. When IGF1SDS rises higher than 3, it is recommended to reduce the GH doses to ensure safety of the treatment [18]. But, a study used titration of IGF1 to treat TS patients, with a mean treatment duration of 6.7 years and the final height of patients increased only 3.2 cm [19].
Our study was the first study to analyze the efficacy and safety of LAGH treatment for TS and discussed the IGF1 levels as part of the efficacy evaluation, to provide basis and references for clinical treatments.

**Subjects and methods**

**Patient**

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 was 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 (0.1mg/kg/w); Group 2 was treated with high-dose LAGH (0.2 mg/kg/w ); Group 3 was control group (daily GH group, 0.38mg/kg/w); Group 4 was untreated control group (untreated or had not been administered GH for up to 3 months), and followed up for 2 years. But in the second year, GH dose of group 1 (0.18mg/kg/w) was increased to similar with Group 2(0.2mg/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 divided into two phases, year 1 with all 4 groups and year 2 with just two, group 2 and group 3.

Analysis the effects of GH therapy, the study flowchart is shown in Fig 1.

LAGH(Jintrolong) is the irreversibly PEGylated LAGH formulation was from GeneScience 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 date included IGF1, glycated hemoglobin (HbA1c), cortisol, free thyroxine (T4), thyroid-stimulating hormone (TSH), lipids, insulin, fasting blood glucose, 2-h postprandial blood glucose, liver, and renal function. GH related side effects including intracranial hypertension, slip-page 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). IGF1SDS 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-t test or one-way analysis of variance (ANOVA). Post hot analysis was performed with the Bonferroni’s adjustment. Chi-square test /Fisher's exact test was used to compare the count data. Paired t-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) was used for statistical analysis. Graphs were plotted using GraphPad Prism version 8.2 (SanDiego, CA).

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 were 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 four groups were well balanced in terms of demographics and clinical characteristics (p>0.05, Table 1). However, BMI was showed differences between groups, (p=0.03, Table 1), but the post hot 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, there was significantly different among 4 groups, (p<0.0001). The treatment groups increased significantly from baseline (p<0.0001) for all, (Table 2; Fig 2 a). and Group 4 was lower than treatment group, there was no difference in untreated group (group 4), (Table 1S), HtSDS increased from baseline between treatment groups, p values for group1, 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 2 b). Comparing the change from baseline (ΔHtSDS) among groups as follows: there was significantly difference between groups, (p=0.0002), (Table 2). Group 2 and Group 3 had higher ΔHtSDS than Group 4, and there was no difference between Group 1 and 4, Group 2 and 3 had higher ΔHtSDS than Group 1, while there was no difference between Group 2 and 3(P>0.99), (Table 1S; Fig 2 c), 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 was shown in Fig 3, compared to the baseline, the levels of IGF1SDS improved, and rapidly reached its peak between 6 to 9 months among treatment groups, and then reached a plateau. IGF1 level 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 patient (21%) in group 2, 5 patient (33%) in group 3 had IGF1 levels >2SD, and in which only 3 patient (7.1%) in group 2, 1 patient (7.7%) in group 3 had IGF1 levels >3SD.

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), compare 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, BA-CA didn’t accelerating.

Complementary Additional Analyses Results

Multivariate correlation analysis in LAGH treatment at first year indicated that ΔHtSDS was positively correlated with baseline variables including baseline dose (r=0.33, p=0.02) and nega-
tively 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). see. (Table 2S)

**Year 2**

Year 2 with just two groups, Group 2 (n=25) and Group 3 (n=7), GH dose of Group 3 (0.45mg/kg/w) was slightly increased than year 1. The baseline HV of group 2 was 3.3±1.5, significant increasing 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), ∆HtSDS 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 compare to that of daily rhGH .

In second year, the mean IGF1 level of 2 groups were 0.9±0.2, 1.9±1.0, p=0.1, 4 patient (16%) in group 2, 1 patient (14.2%) in group 3 had IGF1 levels >3SD, 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 period, there was no serious adverse events occurred, only 4 mild to moderate drug-related adverse events were reported. 1 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. 1 patient from high-dose LAGH group had injection site nodules, and nodules disappeared at follow-up time when the patient changed 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.
**Discussions**

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 0.18mg/kg/w to maintain HV more than 6cm/year. The effect of high-dose LAGH was similar to that of the daily rhGH at a dose of 0.38 to 0.45mg/kg/w through 2-year period. Both two groups showed higher HV and ΔHtSDS 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 monitoring during the full treatment period. We discovered a rapid IGF1 increase and reached its peak between 6 to 9 months among treatment groups, then maintain stable. Most of the IGF1 values within the normal range, only 3 patients (7.1%) in Group 2, 1 patient (7.7%) in Group 3 had got IGF1 levels >3SD at year 1. In the second year, 4 patients (16%) in Group 2, 1 patient (14.2%) in Group 3 had IGF1 levels >3SD, the IGF-1 level between the 2 groups were comparable, the prescribing physician didn’t decrease the GH dose, and IGF-1 levels after transient elevated, decreased or maintain stable at follow-up visits. Our study described 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 relative 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 decrease, but there is a problem should be concerned about, to choose 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 including edema injection-site lipoatrophy etc. No serious side effects occurred in our study. Only 4 mild to moderate drug-related adverse events were reported. 1 patient from low-dose LAGH group had elevating TSH level, and normal free T3 level,
and TSH returned to normal at follow up time after thyroxine supplementation, TS are suscep-
tible to immune diseases, including thyroid disease. So, whether or not beginning growth hormone
therapy, it’s 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. and 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 lipoatro-
phy occurred, when change the injection-site and avoid repeated injections on the same site, in-
jection-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 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 dura-
tion and higher initial GH dose, may result in relative better outcomes[27]. In our study, multi-
variate correlation analysis of LAGH treatment came to a similar conclusion, which was consis-
tent with the relevant studies of daily rhGH. We also found that the therapeutic response in year
1 was positive correlated with baseline IGF1, HiSDS, 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 emphasized the impor-
tance of weight control.

Compared with previous studies, our study found several correlation factors affecting the effi-
cacy of LAGH were as follows: in year 1, patients with younger baseline age, younger bone age
and higher IGF1SDS 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 regiments. 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.

**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 (0.2mg/kg/w) was similar compared with daily rhGH (0.38 to 0.45mg/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 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 was no serious adverse effects. For TS, short-term LAGH treatment was effective and safe.

**Strengths and Limitations**

The fairly large size of the study cohort and first-time evaluation efficacy of LAGH in TS. 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.

**References**


Legends

Table 1. Clinical Characteristics of Study Subjects at Baseline.

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

Table 1S. Post hot analysis of ΔHtSDS, HV was performed with the Bonferroni’s adjustment.

Table 2S. Multivariate correlation analysis between ΔHtSDS, HV at year 1 and baseline variables.

Figure 1 The study flowchart.

Figure 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 (ΔHtSDS) among groups.

Figure 3 The trend of mean insulin-like growth factor 1 standard deviation score (IGF1SDS) at visit time between GH treatment groups (group 1 to 3).
Table 1 Baseline Characteristics of the patients with TS

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>27</td>
<td>14</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>GH dose</td>
<td>0.1</td>
<td>0.2</td>
<td>0.38</td>
<td>0</td>
<td></td>
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<tr>
<td>Chronological age(year)</td>
<td>7.8±2.4</td>
<td>8.0±3.2</td>
<td>8.9±3.1</td>
<td>7.9±3.7</td>
<td>0.75</td>
</tr>
<tr>
<td>Karyotype, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>45, X0</td>
<td>5[25%]</td>
<td>7[25%]</td>
<td>3[20%]</td>
<td>1[7.7%]</td>
<td></td>
</tr>
<tr>
<td>X abnormal</td>
<td>13[65%]</td>
<td>17[61%]</td>
<td>7[53%]</td>
<td>1[76.9%]</td>
<td></td>
</tr>
<tr>
<td>Mosaic</td>
<td>2[10%]</td>
<td>3[11%]</td>
<td>4[27%]</td>
<td>2[15.4%]</td>
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<tr>
<td>Y chromosome material</td>
<td>0</td>
<td>1[3%]</td>
<td>0</td>
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<tr>
<td>Height (cm)</td>
<td>109.6±11.6</td>
<td>109.2±14.0</td>
<td>115.3±17.0</td>
<td>109.5±16.9</td>
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<tr>
<td>HtSDS</td>
<td>-3.23±0.52</td>
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<td>-3.23±0.79</td>
<td>0.60</td>
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<tr>
<td>MPHSDS</td>
<td>0.39±0.57</td>
<td>0.51±0.93</td>
<td>0.29±0.69</td>
<td>0.85±0.91c</td>
<td>0.32</td>
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<tr>
<td>Weight (kg)</td>
<td>22.58±8.17</td>
<td>21.00±8.49</td>
<td>25.91±10.77</td>
<td>19.57±6.97</td>
<td>0.23</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>18.2±3.5</td>
<td>17.0±2.9</td>
<td>18.5±2.6</td>
<td>15.7±1.5</td>
<td>0.03</td>
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<tr>
<td>IGF-1 SDS</td>
<td>-1.10±1.24</td>
<td>-1.10±1.35</td>
<td>-0.72±0.80</td>
<td>-1.15±1.17</td>
<td>0.44</td>
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<tr>
<td>HV (cm/year)</td>
<td>3.2±1.1</td>
<td>3.9±1.5</td>
<td>3.4±0.9</td>
<td>3.9±1.4</td>
<td>0.18</td>
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<tr>
<td>BA (year)#</td>
<td>6.8±2.5</td>
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<td>8.2±3.2</td>
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<td>BA-CA (year)#</td>
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<td>-1.3±1.0</td>
<td>-1.3±1.1</td>
<td>-1.2±1.1</td>
<td>0.19</td>
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</table>


# 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 1S. Post hoc analysis of ΔHtSDS. HV was performed with the Bonferroni’s adjustment.

<table>
<thead>
<tr>
<th></th>
<th>Mean Diff</th>
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<th>Significant</th>
<th>Adjusted P Value</th>
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<td><strong>HV</strong></td>
<td></td>
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<td></td>
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<tr>
<td>group 1 vs. 2</td>
<td>-1.5</td>
<td>-3.14 to 0.16</td>
<td>ns</td>
<td>0.10</td>
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<tr>
<td>group 1 vs. 3</td>
<td>-0.9</td>
<td>-2.85 to 1.09</td>
<td>ns</td>
<td>&gt;0.9999</td>
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<tr>
<td>group 1 vs. 4</td>
<td>2.1</td>
<td>0.13 to 4.09</td>
<td>*</td>
<td>0.03</td>
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<tr>
<td>group 2 vs. 3</td>
<td>0.6</td>
<td>-1.22 to 2.44</td>
<td>ns</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>group 2 vs. 4</td>
<td>3.6</td>
<td>1.77 to 5.43</td>
<td>****</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>group 3 vs. 4</td>
<td>3.0</td>
<td>0.86 to 5.12</td>
<td>**</td>
<td>0.0018</td>
</tr>
<tr>
<td><strong>ΔHtSDS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>group 1 vs. 2</td>
<td>-0.2</td>
<td>-0.64 to 0.15</td>
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<td>0.57</td>
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<td>-0.85 to 0.12</td>
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<td>0.11</td>
</tr>
<tr>
<td>group 2 vs. 3</td>
<td>-0.1</td>
<td>-0.57 to 0.33</td>
<td>ns</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>group 2 vs. 4</td>
<td>0.7</td>
<td>0.23 to 1.11</td>
<td>***</td>
<td>0.0006</td>
</tr>
<tr>
<td>group 3 vs. 4</td>
<td>0.8</td>
<td>0.26 to 1.31</td>
<td>***</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

HV: height velocity. ΔHtSDS: change in HtSDS from baseline. ns: no significance.
Table 2 Comparison of HtSDS, △HtSDS, HV between groups in TS at year 1

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>p(ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>27</td>
<td>14</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>HV</td>
<td>6.7±1.8</td>
<td>8.4±1.9</td>
<td>7.7±2.4</td>
<td>4.7±1.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HtSDS at baseline</td>
<td>-3.23±0.52</td>
<td>-3.46±0.96</td>
<td>-3.27±0.89</td>
<td>-3.23±0.79</td>
<td>-</td>
</tr>
<tr>
<td>HtSDS at year 1</td>
<td>-2.86±0.62</td>
<td>-2.91±1.22</td>
<td>-2.69±0.76</td>
<td>-3.33±0.87</td>
<td>-</td>
</tr>
<tr>
<td>△HtSDS</td>
<td>0.31±0.42</td>
<td>0.56±0.43</td>
<td>0.68±0.69</td>
<td>0.12±0.44</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

HV: height velocity. △HtSDS: change in HtSDS from baseline.
Table 2S. Multivariate correlation analysis between ∆HtSDS, HV at year 1 and baseline variables in LAGH treatment group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>∆HtSDS</th>
<th></th>
<th></th>
<th></th>
<th>HV</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>r (95%CI)</td>
<td>p</td>
<td></td>
<td>r</td>
<td>r (95%CI)</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>GH dose</td>
<td>0.33</td>
<td>0.04 to 0.56</td>
<td>0.02</td>
<td></td>
<td>0.36</td>
<td>0.06 to 0.59</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>CA (year)</td>
<td>-0.32</td>
<td>-0.55 to -0.03</td>
<td>0.03</td>
<td></td>
<td>-0.67</td>
<td>-0.80 to -0.47</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>BA</td>
<td>-0.54</td>
<td>-0.72 to -0.28</td>
<td>0.0002</td>
<td></td>
<td>-0.71</td>
<td>-0.83 to -0.51</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.08</td>
<td>-0.33 to 0.18</td>
<td>0.55</td>
<td></td>
<td>-0.36</td>
<td>0.59 to -0.07</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>HtSDS</td>
<td>0.18</td>
<td>-0.11 to 0.44</td>
<td>0.24</td>
<td></td>
<td>0.33</td>
<td>0.03 to 0.57</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>MPH SDS</td>
<td>0.09</td>
<td>-0.19 to 0.37</td>
<td>0.54</td>
<td></td>
<td>0.15</td>
<td>-0.12 to 0.40</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

HV: height velocity; ∆HtSDS: change in HtSDS from baseline; CA: chronological age; BA: bone age; BMI: body mass index; MPH: mid-parental height; SDS: standard deviation score.
Prepuberty children with TS were assessed for eligibility (n=75)

Group 1 (n=20)  
LAGH 0.1 mg/kg/w

Group 2 (n=27)  
LAGH 0.2 mg/kg/w

Group 3 (n=14)  
Daily GH 0.38 mg/kg/w

Group 4 (n=13)  
Untreated control group

Analysis the effects of GH therapy at year 1

Group 1  
LAGH 0.18 mg/kg/w  
Lost to follow-up (n=2)

Group 2  
LAGH 0.2 mg/kg/w  
Lost to follow-up (n=2)

Group 3  
Daily GH 0.45 mg/kg/w  
Lost to follow-up (n=7)

Group 4  
Began GH therapy (n=9)  
Lost to follow-up (n=4)

Analysis the effects of GH therapy at year 2
IGF-1SDS (mean)

Visit, months

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1, n = 20</td>
<td>-1.1±1.2</td>
<td>-0.6±0.3</td>
<td>-0.23±1.1</td>
<td>-0.2±1.4</td>
<td>0.3±1.2</td>
</tr>
<tr>
<td>Group 2, n = 27</td>
<td>-1.1±1.4</td>
<td>0.4±1.2</td>
<td>0.5±1.2</td>
<td>0.3±1.4</td>
<td>0.9±1.4</td>
</tr>
<tr>
<td>Group 3, n = 11</td>
<td>-0.7±0.8</td>
<td>0.9±0.4</td>
<td>1.8±0.9</td>
<td>2.7±0.3</td>
<td>1.6±0.7</td>
</tr>
</tbody>
</table>