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RESEARCH ARTICLE

Clinical evaluation of recombinant human growth hormone injection in children with growth hormone deficiency

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Abstract Recombinant human growth hormone (rhGH) has been widely used in the clinical treatment of growth hormone deficiency. To simplify the injection process and increase drug compliance, application of the GH injection has become a new treatment plan in recent years. The purpose of the current study was to evaluate the efficacy and safety of rhGH injection for the treatment of growth hormone deficiency (GHD) in children in China. In a nationwide, noncomparative, prospective, randomized, open trial, 31 children with confirmed complete GHD received subcutaneous injection of rhGH at 0.25 mg/kg·wk (0.107 IU/kg·d). The injection was given daily and the total weekly amount was separated into 6–7 injections. The patients were followed up at 3-month intervals and the treatment duration was 12 months. The height (HT), annual growth velocity (GV), mean height standard deviation score (HT SDS), blood serum insulin-like growth factor I (IGF-I), insulin-like growth factor binding protein 3 (IGFBP-3), and bone maturity before and after treatment were compared, and the safety of the treatment was analyzed. The mean HT, GV, and HT SDS were increased from 109.0±14 cm, 2.7±0.9 cm/yr, and −4.62 ±1.46 at baseline to 121.8±13.4 cm, 12.9±3.3 cm/yr, and −2.47±1.86 after 12 months of treatment, respectively ($P < 0.001$). At the same time, blood IGF-I and IGFBP-3 were increased significantly [41.27±64.43 μg/L *vs* 159.21±167.92 μg/L and 1540.00±1325.11 mg/L *vs* 3533.93±1413.82 mg/L, respectively ($P < 0.001$)]. The bone age assessments performed 6 and 12 months after the treatment showed that no advanced bone maturation was noted. No serious adverse events occurred during the treatment, and the drug-related adverse events were mainly decreased thyroid function. We conclude that rhGH injection is a safe and effective drug for treatment of growth hormone deficiency in children.

Keywords recombinant human growth hormone; injection; growth hormone deficiency

1 Introduction

Patients with growth hormone deficiency (GHD) rely on growth hormone (GH) replacement therapy. Recombinant human growth hormone (rhGH) has been successfully synthesized and massively produced since the human GH gene was obtained using bio-engineering recombinant DNA techniques in the early 1980s and was transduced into prokaryotic or eukaryotic cells [1]. For more than 20 years, rhGH lyophilized powder for injection has been widely used in the clinical treatment of GHD and achieved satisfying therapeutic results [2–10]. However, rhGH lyophilized powder for injection requires to be dissolved before injection, which is complex and may cause a risk to the children, thus affecting drug compliance and efficacy [11]. To increase drug compliance, application of the GH injection through a simplified injection process has become a new treatment plan. In recent years, the rhGH injection has been gradually applied in clinical practice in Europe, the US, and Japan. The rhGH injection (Jintropin® AQ) was approved by the State Drug Administration (SDA) in China in 2005 and has been used for the treatment of

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children with GHD. The current study was a nationwide, multi-center, randomized, open trial using the rhGH injection to treat strictly screened children with GHD for 1 year. The efficacy and safety of the rhGH injection were further evaluated.

2 Subjects and methods

2.1 Subjects

Thirty-one patients were enrolled between April and August 2006, who were recruited from Tongji Hospital (Wuhan, China), the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China), Beijing Children's Hospital of the Capital Medical University (Beijing, China), Children's Hospital of the Medical College of Zhejiang University (Hangzhou, China), the First Hospital of Jilin University (Changchun, China), and the Children's Hospital of Fudan University (Shanghai, China). The average age of the patients was 10.5±4.1 years. There were 11 girls and 20 boys. The average body weight was 19.6±5.9 kg. All patients were in Tanner stage I, and the bone age/actual age (BA/CA) was 0.53±0.12. Pituitary magnetic resonance imaging (MRI) scans showed 13 cases with normal pituitaries and 18 cases of small pituitaries and dysplasia. All children met the following criteria: (1) GHD was confirmed based on the medical history, clinical symptoms and physical signs, GH stimulation test results, and imaging studies before treatment [specifically, the absolute height was 2 standard deviation (SD) lower than the average height of healthy children of the same age and gender based on statistical data of children in 9 cities of China in 1995 [12]; the growth velocity (GV) was ⩽ 4.0 cm/yr; the GH stimulation test with two different drugs confirmed that the peak plasma GH in the child was < 7.0 ng/mL; and the bone age (BA) was ⩽9 years of age for girls, ⩽10 years of age for boys, and > 2 years younger than the actual age]; (2) pre-puberty (Tanner I stage) children > 3 years of age with no gender limitations; (3) children who have not previously received GH treatment; (4) birth weight > 2500 g; and (5) all children underwent complete blood/urine screening, electrocardiogram, liver and kidney function tests, hepatitis B virus screening, thyroid function tests, cortisol determination, and pituitary MRI examination before treatment. Patients with serious heart or lung diseases, blood dyscrasias, malignant tumors, systemic infections, impaired immune function, or mental disease were excluded. Patients with positive hepatitis B core antibody, hepatitis B surface antigen, and hepatitis B e antigen were excluded. Patients with other types of abnormal growth and development were excluded, including Turner syndrome, constitutional delay of growth and puberty (CDGP), and Laron syndrome.

2.2 Methods

2.2.1 Treatment observation

This study was a randomized, multi-center, open trial. The selected children were correctly injected with Jintropin® AQ (Changchun Kinsey Pharmaceutical Co., Ltd., Changchun, China), with appropriate training. The subcutaneous injection was performed once daily before going to bed at night; the dose was 0.25 mg/kg·wk (0.107 IU/kg·d) and the total weekly amount was separated into 6–7 injections. The injection sites included the upper arms, thighs, and periumbilical area. The patients were followed up every 3 months. During the same time period in the morning, the height and weight were measured and the blood was drawn to detect liver and kidney function, alkaline phosphatase, calcium, phosphorus, blood lipids, glycosated hemoglobin A1c (HbA1c), insulin, fasting blood glucose, 2-h postprandial trace blood sugar, thyroid function, blood serum insulin-like growth factor I (IGF-I), insulin-like growth factor binding protein 3 (IGFBP-3), and anti-hGH antibodies. An electrocardiogram (ECG) was also performed. Radiographs of the wrist bone were obtained after 6 and 12 months of treatment, and the bone age was accurately analyzed by specialists using the TW2 (Tanner–Whitehouse 2nd edition) method. IGF-I and IGFBP-3 were measured using the enzyme-linked immunosorbent assay (ELISA) method at the Pediatric Endocrinology and Metabolism Research Lab of Tongji Hospital (the kit was provided by DSL Co., USA). Serum anti-hGH antibody was measured using the radioimmunoassay method at Beijing Northern Institute of Biotechnology (China).

2.2.2 Method of evaluation

The primary outcome measure was performed to compare the annual GV (cm/yr) of the children with GHD before treatment and 3, 6, 9, and 12 months after treatment. GV = 12×(height at the end of treatment – height at the start of treatment) (cm) / treatment duration (months). The secondary outcome measures were as follows: (1) to compare the HT standard deviation score (SDS) (HT SDS = [HT–mean HT] / SD) of the actual age before and after treatment, in which the mean HT and SD are the mean height and standard deviation of the normal children of the same age and gender (the statistical data of the 1995 physical development survey in 9 major Chinese cities were used as the standard); (2) biochemical indicators with predictive value (IGF-I and IGFBP-3); and (3) bone maturity after 6 and 12 months of treatment (the change in bone age/the change in actual age [ΔBA/ΔCA]). The safety indices included abnormal clinical symptoms, vital signs, and laboratory and imaging examinations.

2.3 Statistical analysis

All statistical analyses were performed using Professional SAS 8.1 statistical analysis software. The data are shown as $\bar{x} \pm s$ or the median (M) and range (minimum-to-maximum). A paired *t*-test or signed rank test was used for comparisons of the changes in quantitative data within the group before and after treatment. The changes of the two groups compared with the baseline were compared using the analysis of covariance model. For categorical data, the χ^2 test, including the CMH χ^2 test (Cochran-Mantel-Haenszel χ^2 test), or the Fisher's exact test was used to compare the two groups.

3 Results

3.1 Completion rate

Thirty-one patients showed good drug compliance and completed the clinical trial.

3.2 Changes in the observation indices before and after treatment

3.2.1 Height growth

The height growth showed a good linear increase in 31 children after 3, 6, 9, and 12 months of treatment. The height growth, annual GV, and HT SDS were increased significantly compared with the baseline. The annual GV increased significantly from 2.7±0.9 cm/yr before treatment ($P < 0.001$; Tables 1 and 2). The most significant height growth occurred after 3 months of treatment and the growth rate slightly decreased with the increase in the treatment time.

Table 1 Changes in the growth efficacy indices in children with GHD before and after treatment

follow-up time	annual height growth/cm	annual growth velocity/cm·yr^{-1}	mean height standard deviation score
before treatment	109.0±14.1	2.7±0.9	– 4.62±1.46
after treatment			
3 months	113.4±14.1	16.0±5.1	– 3.80±1.53
6 months	116.3±13.7	14.1±4.0	– 3.28±1.60
9 months	119.3±13.1	13.7±3.5	– 2.86±1.75
12 months	121.8±13.4	12.9±3.3	– 2.47±1.86
F value	6.14	115.36	22.71
P value	< 0.001	< 0.001	< 0.001

Data were presented as $\bar{x} \pm s$. The means before treatment were compared with the means at each time point after treatment for each variable and the differences were statistically significant ($P < 0.0001$). GHD: growth hormone deficiency.

Table 2 Baseline correction of the growth efficacy index changes in children with GHD after treatment

follow-up time	annual height growth/cm	annual growth velocity/cm·yr^{-1}	mean height standard deviation score
after treatment			
3 months	4.0±1.3	13.3±5.0	0.68±0.33
6 months	7.0±2.0	11.4±4.0	1.20±0.56
9 months	10.3±2.6	11.0±3.5	1.76±0.79
12 months	12.9±3.3	10.2±3.3	2.21±0.97

Data were presented as $\bar{x} \pm s$. GHD: growth hormone deficiency.

3.2.2 Changes in blood IGF-I and IGFBP-3

The serum levels of IGF-I and IGFBP-3 were increased significantly after 3, 6, 9, and 12 months of treatment and the differences were statistically significant compared to those before treatment ($P < 0.001$), suggesting that the height increase, IGF-I, and IGFBP-3 were significantly activated to relatively higher levels by the medication. The increases were especially obvious after 3–6 months of treatment and decreased slightly on the 9th month. With continuous treatment, the height growth was increased slightly in the 12th month. Overall, the levels of IGF-I and IGFBP-3 were stable after 3 months of treatment (Table 3).

Table 3 Changes in IGF-I and IGFBP-3 before and after treatment

follow-up time	IGF-I/μg·L^{-1}	IGFBP-3/mg·L^{-1}
before treatment	41.27±64.43	1540.00±1325.11
after treatment		
3 months	179.15±155.03	3891.18±1815.36
6 months	202.32±141.34	4051.47±1308.51
9 months	156.75±155.48	3408.93±1435.85
12 months	159.21±167.92	3533.93±1413.82
F value	3.52	8.79
P value	< 0.001	< 0.001

Note: Data were presented as $\bar{x} \pm s$. The means of each variable before treatment were compared with the means at each time point after treatment and the differences were statistically significant ($P < 0.0001$).

3.2.3 Bone maturity at the end of treatment (ΔBA/ΔCA)

The bone age of the children before treatment significantly lagged behind the actual age (the BA/CA was 0.53±0.12). The bone age assessments on the 6th and 12th months showed that the bone maturity (ΔBA/ΔCA) was 1.01±0.57 and 1.07±0.75, respectively, suggesting that there was no accelerated development of the bone age and that the growth hormone treatment did not promote the accelerated increase in bone age.

3.3 Safety indices

No serious adverse events occurred in the 31 children. There was 1 child with a mild headache during treatment, and the symptom was alleviated the next day. There was 1 child with eyelid edema, and the child got well within 1 month without any treatment. The abnormal treatment-related laboratory results were as follows: decreased thyroid function existed in 5 patients, which returned to normal after an average of 3 months of treatment with levothyroxine tablets; there were 4 cases of elevated alkaline phosphatase (with an average increase of 133 U/L compared to the value before treatment) and 2 cases of elevated triglycerides, of which 1 case showed combined hypothyroidism after 10–12 months of treatment and the other case showed slightly increased triglycerides (increased by 0.4 mmol/L) compared to that before treatment; 2 patients experienced a slight increase in aspartate transaminase (AST) (with an average increase of 17 U/L compared to that before treatment) and recovered spontaneously; and the serum calcium and phosphate levels, renal function, insulin, fasting blood glucose, 2-h postprandial blood glucose, HbA1c, and ECG were normal in all children during the treatment, and the serum anti-hGH antibody titers were negative.

4 Discussion

rhGH has been used in clinical practice for more than 20 years since its successful synthesis and mass production in 1985. A large number of studies have confirmed that rhGH is safe and effective for the treatment of GHD in children [13–17]. Bryant *et al*. [18] systematically evaluated 32 randomized controlled studies that used GH, and the results showed that GH treatment can accelerate short-term growth and the growth rate can be increased by 0–1.0 SD within 1 year compared to healthy children of the same age and gender. The ultimate height can be increased by 2–11 cm compared to children without any treatment. In the Kabi International Growth Study (KIGS), more than 62 000 children with GHD received GH treatment around the world, and similar results were obtained [19]. The price of GH is very high and the dissolving process of the rhGH lyophilized powder for injection is relatively complex, which may result in a certain degree of psychological burden for the patients and their parents. Therefore, a simple injection method has been developed based on the demand.

Currently, most rhGH production employs *Escherichia coli* (*E. coli*) as the expression system. The non-glycosylated single strand consisting of 191 amino acids is produced by a recombinant technique, which has the same amino acid sequence as the GH secreted by the anterior pituitary [20]. After the protein liquid stability technique is applied, the GH molecules can be preserved stably in liquid for a long time in its natural structure without being freeze-dried. In 1995, a genetic engineering technology company (Genentech, USA) received FDA approval and produced the first vial of human GH solution (Nutropin AQ®), which has been applied successfully in patients with GHD, idiopathic short stature, small for gestational age, and chronic renal failure. Nutropin AQ® received approval from the European Union in 2001 and then has been widely used for the treatment of GHD in Europe. Norditropin® SimpleXx®, produced by Novo Nordisk, combined the GH solution with the injection pen apparatus for the first time in 1997 and has been used in patients with GHD in the US, Europe, and Japan [21]. Jintropin® AQ was approved by the State Drug Administration (SDA) in 2005 and has been formally applied in the clinical treatment of children with GHD in China. However, strict long-term clinical research has been very limited.

In the current study, 31 strictly screened pre-puberty patients with GHD received rhGH solution treatment. After 1 year of treatment, the children's heights were significantly increased and showed good linear growth, which reflected catch-up growth. With respect to height increase indices, the height growth, annual GV, and HT SDS were increased significantly compared with the baseline. During the course of treatment, the increase was most obvious at 3 months after treatment. As treatment time went on, the growth rate was decreased slightly. The GV reached a peak value after 36 months of treatment and slightly decreased after 6–12 months of treatment. The HT SDS was increased continuously, indicating that the height difference between the patients and the normal children of the same age and gender was decreased gradually. The height was increased by 2.2 SD after 12 months of treatment. Iyoda *et al*. reported [22] that the HT SDS was increased from –2.6 SD to –2.1 SD after 12 months of GHD solution treatment. The difference between the current study and their study may have been attributed to the children in our study being at Tanner I stage of puberty, and the bone age requirement before the treatment was stricter in this study.

GH does not promote the growth of long bones by direct effects alone; GH mainly stimulates the precartilage cells or the germinal cells in the epiphyseal growth plate to differentiate into cartilage cells and promotes IGF-I gene expression in those cells. GH acts on IGF-I receptors of differentiated cartilage cells *via* autocrine and paracrine pathways, causing clone amplification and hypertrophy of chondrocytes and the formation of osteoblasts; thus, bone growth is promoted. The main effects of IGF-I are to promote the differentiation and proliferation of bone cells and to further promote the linear growth of the body. IGFBP-3 is a binding protein of IGF-I, and the levels of IGFBP-3 and IGF-I in the blood may reflect the effects of GH very closely. IGF-I and IGFBP-3 are mainly regulated by GH, the level of which in the blood is relatively stable

without obvious pulse secretion or circadian variation. The IGF-I levels of the children in this group were increased significantly after treatment, which was up to 4–5 times higher than the values before treatment. The IGFBP-3 levels were about 2–3 times higher than those before treatment, indicating that IGF-I and IGFBP-3 are predictive biochemical markers that can reflect growth, which is consistent with previous reports [23,24]. In addition, the data showed that the IGF-I and IGFBP-3 levels were the highest after 3–6 months of treatment and slightly decreased in the 9th month. With continuous treatment, the IGF-I and IGFBP-3 levels were slightly increased again in the 12th month. Overall, IGF-I and IGFBP-3 levels were stable after 3 months of treatment. As IGF-I has an effect on promoting mitosis and anti-apoptosis [25,26], some scholars have suggested that the molar ratio of IGF-I to IGFBP-3 is a safety index that can be used to evaluate the safety of long-term GH use [27,28]. The ratio of IGF-I to IGFBP-3 increased in both GHD and non-GHD children after treatment with routine doses of GH, but no statistically significant difference was found between the two groups.

GH can accelerate growth and development; the growth of patients was slow before treatment, the annual GV was < 4 cm/yr, and the bone age significantly lagged behind the actual age. The bone age did not show accelerated development when the growth was accelerated in the 6th and 12th months, which suggests that the GH solution did not accelerate the increase in bone age; this is consistent with the effects of the lyophilized powder for injection on bone maturity [29].

In recent years, with the rapid development of genetic engineering, the GH product obtains a very high purity. Although the medication is administered with a non-pulse injection, the local and systemic reactions are rare and the safety is good. The relatively common side effects are local redness and swelling at the injection site, headaches, vomiting, and peripheral edema. The common biochemical changes of the laboratory examination are hypothyroidism and temporarily impaired glucose tolerance. There were no serious adverse events in the 31 children of this group after treatment. There was a case of mild headache and a case of eyelid edema during treatment, and the symptoms were relieved spontaneously within 1 week, after a low-salt diet was suggested. The main treatment-related laboratory abnormalities included 5 cases of decreased blood T4 without any clinical symptom, and the T4 returned to normal level after levothyroxine tablets were administered, which was consistent with the diagnosis of subclinical hypothyroidism, but the reason was still not clear. It may be related to the increased consumption of T4 caused by the growth acceleration or the deiodination of T4 by the tissue outside of the thyroid gland and the corresponding increase in T3 [30]. There were 4 cases of elevated alkaline phosphatase (ALP) levels. ALP is an index reflecting osteoblast activity, and an increase suggests accelerated bone transformation. Serum anti-hGH antibodies were negative in the patients during the follow-up period of treatment.

In summary, the rhGH injection has definite therapeutic effects for treatment of children with GHD, which can significantly promote bone growth without accelerating bone age changes. The medication extraction and injection methods are simple, and drug compliance in children is good. Regular follow-up should be conducted to observe changes in height, weight, and the bone age of children during treatment, and the changes in thyroid function, ALP, glucose, and lipid metabolism should be closely monitored to make sure that the long-term treatment is safe and effective.

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