Efficacy and safety of growth hormone treatment in Japanese children with small-for-gestational-age short stature in accordance with Japanese guidelines

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Abstract. The efficacy and safety of recombinant human GH (rhGH) treatment were assessed in Japanese children with small-for-gestational-age short stature. A total of 88 patients were enrolled in the comparative and extension studies. At the end of the comparative study (24 mo), the mean height SD score for chronological age had significantly increased in the 0.23 mg/kg/wk and 0.47 mg/kg/wk groups with increments of 0.84 ± 0.42 and 1.50 ± 0.44 SD, respectively. In the extension study, the dose could be increased based on the pre-defined growth criteria. Increments in height SD scores over the 24 to 36 mo period at doses of 0.23 mg/kg/wk, 0.23 to 0.47 mg/kg/wk, and 0.47 mg/kg/wk were 0.25 ± 0.28, 0.46 ± 0.21, and 0.28 ± 0.16 SD, respectively. The growth effect increased following dose escalation even in the low responders in the initial 2-yr treatment at 0.23 mg/kg/wk, indicating the effectiveness of dose escalation in accordance with the Japanese guidelines. rhGH at 0.47 mg/kg/wk provided a greater degree of growth promotion after 24 mo. The safety profile appeared to be tolerable and was similar in all groups. Considering the increased insulin resistance, the recommendations of the regulatory authorities should be followed to minimize the risks of rhGH treatment.

Key words: recombinant human GH, small for gestational age, short stature, GH treatment, guideline

Introduction

GH is a protein that is synthesized and secreted by the anterior pituitary gland and promotes growth in children. GH deficiency causes growth failure, and recombinant human GH (rhGH) is often administered to treat this condition. rhGH is also successfully used to treat other cases of growth failure such as small-for-gestational age (SGA), Turner’s syndrome, and
chronic renal insufficiency.

SGA is defined as a condition when birth weight and height are lower than expected for the gestational age. Approximately 90% of infants born SGA catch up their height in the first 2 yr; however, most of those who do not catch up by the age of 2 are likely to remain short during childhood, a condition that is called SGA short stature (1, 2). It is reported that SGA short stature accounts for about 20% of adults with short stature (3). Treatment with rhGH has been shown to be effective in patients with SGA short stature, and its clinical application was approved in the U.S. in 2001, the E.U. in 2003, and Japan in 2008. Since GH treatment of patients with SGA short stature is not a mere replacement therapy, a treatment guideline and recommendations for rhGH treatment in SGA have been provided by the Japanese Society for Pediatric Endocrinology and the Japan Society for Premature and Newborn Medicine (4, 5) in 2007 to ensure its appropriate administration.

In this paper, we report the efficacy and safety results when rhGH was administered in accordance with these guidelines to children born SGA who did not show a catch-up in growth in height by the age of 3, unlike 2 preceding Japanese studies, whose protocols did not follow the guidelines (6, 7).

**Materials and Methods**

We report the results of a dose-comparative study (Part 1) and a follow-up extension study (Part 2) to show the efficacy and safety of rhGH (GROWJECT®) in patients with SGA short stature, sponsored by JCR Pharmaceuticals Co., Ltd. in Japan. This study was conducted in accordance with the ethical considerations of the Declaration of Helsinki and in compliance with the Good Clinical Practice regulations. Prior to the initiation of the study, the study protocol was approved by each local Institutional Review Board. The study design and potential adverse drug reactions were fully explained to the patients and their guardians, and written informed consent was obtained before the initiation of the study.

**Subjects**

Forty-five male and 43 female children who met the following criteria were enrolled in this study:

1) Subjects with birth weight and height below the 10th percentile of gestational age-equivalent reference values
2) Subjects with either birth weight or height below −2.0 SD of gestational age-equivalent reference values
3) Subjects with a chronological age at the initiation of rhGH treatment of 3 yr or more but less than 8 yr for boys and 7 yr for girls
4) Subjects who had not developed secondary sexual characteristics yet (Tanner Stage 1)
5) Subjects with height SD score (SDS) for chronological age at the time of screening examination of less than −2.5 SD
6) Subjects with available height data for 12 mo prior to the screening examination
7) Subjects with growth velocity SDS for chronological age during the 12 mo before the screening examination of less than 0 SD
8) Subjects with a peak GH level of > 6 ng/mL in a GH stimulation test (or peak GH level of > 16 ng/mL in the GH-releasing peptide 2 [GHRP-2] load test)
9) Subjects with a guardian (legal representative) who could provide written informed consent

Patients with the following diseases and disorders were excluded from the study: endocrine disorders that might cause short stature, chromosomal abnormalities and malformation syndromes (including Silver-Russell syndrome), bone diseases such as a-/hypo-chondroplasia, a past medical history of radiation therapy or chemotherapy, severe cardiac diseases, kidney diseases, liver diseases, diabetes, or other chronic diseases.
Study design

This report includes 2 studies, a dose-comparative study (Part 1) and a follow-up extension study (Part 2) up to 46 mo. Subjects were randomized to receive either the low dose (0.23 mg/kg/wk) or the high dose (0.47 mg/kg/wk) of rhGH for 24 mo in Part 1.

After completion of the 24-mo 2-dose comparative study, subjects who were willing to participate in the extension study (Part 2) were enrolled and received treatment with rhGH for up to 46 mo after initiation of the dose-comparative study. Among the subjects who received the low dose of rhGH during the dose-comparative study (Part 1), those without signs of puberty meeting the follow-up dose escalation criteria were eligible to receive an escalated dose of 0.47 mg/kg/wk during the extension study (Part 2) in accordance with Japanese guidelines (4, 5).

Dose escalation criteria

The Japanese guideline is shown in Fig. 1. Subjects who received a low dose of GH during the dose comparative study (Part 1) were divided into 2 groups at each time point shown in Fig. 1 in the extension study (Part 2) on the basis of the above criteria. Those who met the criteria were assigned to the increased-dose group and received a high dose; and those who did not meet the criteria were assigned to the dose-maintenance group and were continuously treated at the same low dose used in Part 1.

Anthropometric and bone age measurements

Height SDS for chronological age was calculated using the Japanese children’s mean and SD values by sex and age (8). Growth velocity SDS for chronological age was calculated using the Japanese children’s mean and SD values by sex and age, as reported by Suwa et al. (9). Bone
age was evaluated by an independent specialized physician based on X-ray images of the wrist; the names of the study sites and subjects were blinded. The Japanese standardized TW2 (RUS) method (10) was used in the case of bones from children 3 yr or older. For children younger than 3 yr, the original TW2 method was used, because the Japanese standardized TW2 (RUS) method was not available for this age.

Psychosocial characteristics (Questionnaire survey)

Psychosocial characteristics were evaluated at the initiation of rhGH treatment and at 12, 24, and 36 mo using the Pediatric Psychosomatic and Behavioral Checklist developed by Osada et al (11).

Statistical methods

The primary efficacy analysis compared changes in the height SDS (Δ height SDS) for chronological age during the first 24 mo of rhGH treatment between the low- and high-dose groups (Part 1). A paired t-test was used to compare the Δ height SDS for chronological age within each group, and a t-test was used for comparisons between groups. Wilcoxon’s signed-rank test was used to compare psychosocial characteristics within each group. For all comparisons, the level of statistical significance was \(p < 0.05\).

Results

Baseline characteristics of subjects

Forty-three patients (boys: 22; girls: 21) and 45 patients (boys: 23; girls: 22) were allocated to the low-dose and high-dose groups, respectively. The subjects’ baseline characteristics are summarized in Table 1. The extension study (Part 2) was conducted in compliance with the Japanese guideline, which allows for a dose increase every 6 mo. In this study, the dose was increased at 24 mo after the start of rhGH treatment in 21 subjects, at 30 mo in 4 subjects, and at 36 mo in 1 subject. The dose was not increased in any additional subjects. Finally, 26 of the 43 subjects in the low-dose group were allocated to the increased-dose group. In this report, all patients administered an increased dose in each period were analyzed as the increased-dose group.

Changes in the height SDS for chronological age

Table 2 shows height SDS for chronological age, and changes in the height SDS for chronological age, from the initiation of rhGH treatment (Δ height SDS for chronological age).

The Δ height SDS for chronological age at 24 mo increased by 0.84 ± 0.42 SD in the low-dose group and by 1.50 ± 0.44 SD in the high-dose group; a statistically significant difference was confirmed between the 2 groups (\(p < 0.001\)).

At the final assessment point, the height SDS for chronological age was −1.78 ± 0.71 SD in the dose-maintenance group, −1.82 ± 0.84 SD in the increased-dose group, and −1.36 ± 0.92 SD in the high-dose group; the mean values in all treatment groups were higher than −2.0 SD, and 70.6% of subjects in the dose-maintenance group, 53.8% of subjects in the increased-dose group, and 80.0% of subjects in the high-dose group reached a normal stature (>−2.0 SD).

The Δ height SDS for chronological age at 24 mo after the initiation of rhGH treatment was 1.12 ± 0.36 SD in the dose-maintenance group and 1.50 ± 0.44 SD in the high-dose group. The Δ height SDS for chronological age at the final assessment point was 1.49 ± 0.54 SD in the dose-maintenance group and 1.89 ± 0.56 SD in the high-dose group. These results indicate that the growth-promoting effects were sustained even in the second year and thereafter.

In contrast, there was also a low-response group (which became the increased-dose group in step 2) in which the subjects did not grow well. The Δ height SDS values of the chronological ages for this group during the initial 12 mo, and the next consecutive 12 mo, were relatively low (0.56 ± 0.30 SD and 0.14 ± 0.17 SD, respectively),
indicating a reduced increase in the height SDS for chronological age after 24 mo. However, a larger increase was noted during the final 12 mo of the 36-mo period (0.46 ± 0.21 SD), demonstrating that dose escalation according to the guidelines can increase the growth-promoting effect, even in subjects with an insufficient response to 2 yr of low-dose treatment.

The IGF-I SDS levels increased rapidly from −0.69 ± 1.28 SD and −0.53 ± 1.08 SD to 0.43 ± 1.26 SD and 1.24 ± 1.45 SD at 1 mo in the low- and high-dose groups, respectively. The levels in the increased-dose group were found to be increased from 0.07 ± 1.29 SD to 0.72 ± 1.51 SD 6 months after dose escalation. Those levels remained stable thereafter (data not shown).

With respect to bone age, no excessive progression was found in any of the groups (Supplementary Fig. 1: online only).

### Psychosocial characteristics (Questionnaire survey)

The guardians of subjects were asked a total of 29 questions contained in the Pediatric Psychosomatic and Behavioral Checklist (11) at the initiation of rhGH treatment and at 12, 24, and 36 mo. The results from this survey showed improvements in the psychosocial characteristics, especially in aspects attributable to short stature (data not shown).

### Adverse events and adverse drug reactions

Tables 3 show the incidences of adverse drug reactions reported in 2 or more subjects...
during the entire study including both the dose-comparative and extension studies. The profile of adverse drug reactions was similar to that reported to be caused by rhGH treatment in previous reports.

### Glucose metabolism

The changes in the HbA1c levels (%) from the initiation of rhGH treatment are shown in Supplementary Fig. 2 (online only). The mean HbA1c values at the initiation of rhGH treatment were within the normal range. Although a marginal, but statistically significant, increase was found after 24-mo rhGH treatment, the HbA1c levels at the end of rhGH treatment remained within the normal range in all of the treatment groups.

An oral glucose tolerance test (OGTT) was performed every 12 months throughout the entire study. A statistically significant, but clinically subtle, increase in the fasting plasma glucose levels compared to those at the initiation of rhGH treatment was found. However, the values remained within the normal range; no subjects had OGTT results suggesting diabetes; furthermore, no subjects were diagnosed as being diabetic.

Changes in fasting plasma immunoreactive insulin (IRI) levels and the changes in sigma IRI levels (the sum of the IRI levels before the glucose load and at 30, 60, 90, and 120 min after the glucose load) were significantly increased compared with the initial levels. (Supplementary Figs. 3 and 4: online only).

### Discussion

First, we will discuss the effect of rhGH treatment in patients with SGA short stature. In this study, among the patients allocated to the low-dose group (0.23 mg/kg/wk), those patients who showed an insufficient Δ height SDS for...
their chronological age during or after the second year were allocated to the increased-dose group (0.47 mg/kg/wk), whereas those patients with a sufficient Δ height SDS for their chronological age over the same period were allocated to the dose-maintenance group (0.23 mg/kg/wk).

It was of note that the growth-promoting effect improved, even in subjects who showed insufficient effects in the second year of treatment, which is a similar finding to that reported by Tanaka et al. who described an increase in the height SDS for chronological age by increasing the dose to 0.47 mg/kg/wk in accordance with the guideline-based second year treatment schedule, even in subjects who showed insufficient effects at an initial dose of 0.23 mg/kg/wk in the first year of treatment (6).

This finding indicates that some patients respond to a low dose of 0.23 mg/kg/wk, and that the non-responders also show an improvement in growth promotion after they receive an increased dose. Therefore, we conclude that after commencing treatment with a low dose, there should be a periodical review of the dose in the initial years and it should be increased based on the growth-promoting response observed to optimize the dose.

It should be noted that because the mean height SDS for chronological age at the initiation of therapy in this study was below −3.0 SD and the mean growth velocity SDS for chronological age before the initiation of the study was below −1.5 SD, the degree of short stature would likely have worsened without treatment in many

| Table 3. Adverse drug reactions that occurred in at least 2 patients in both the dose-comparative and the long-term extension studies |
|---------------------------------------------------------------|
| **Total N** | 88 |
| **Number of subjects with adverse drug reactions** | 58 |
| **Proportion of subjects with adverse drug reactions (%)** | 65.9 |
| **Number of events** | 122 |
| **Adverse drug reactions** | **Preferred term** | **Number of subjects** | **Proportion (%)** | **Number of events** |
| Nervous system disorders | Headache | 4 | 4.5 | 6 |
| Respiratory, thoracic and mediastinal disorders | Tonsillar hypertrophy | 8 | 9.1 | 10 |
| Musculoskeletal and connective tissue disorders | Pain in extremity | 12 | 13.6 | 15 |
| | Arthralgia | 4 | 4.5 | 5 |
| | Arthritis | 3 | 3.4 | 3 |
| | Growing pains | 2 | 2.3 | 2 |
| General disorders and administration site conditions | Injection site haematoma | 6 | 6.8 | 7 |
| | Pyrexia | 2 | 2.3 | 2 |
| Investigations | Glucose tolerance test abnormal | 47 | 53.4 | 76 |
| | Eosinophil count increased | 24 | 27.3 | 26 |
| | Blood creatine phosphokinase increased | 7 | 8 | 12 |
| | Alanine aminotransferase increased | 7 | 8 | 7 |
| | Aspartate aminotransferase increased | 6 | 6.8 | 7 |
| | Blood urine present | 5 | 5.7 | 6 |
| | MedDRA Ver. 12.0. | | | |

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subjects. This study reveals that 2-yr of rhGH treatment in such severe SGA short stature patients with a poor prognosis of growth could improve the height SDS for chronological age.

Second, we will discuss the safety of the rhGH treatment. An analysis of adverse events and adverse drug reactions did not reveal any differences between the dose groups. The adverse drug reactions observed were similar to those previously reported to be associated with rhGH treatment.

With respect to rhGH administration to children with SGA, glucose tolerance has been a concern because GH has anti-insulin effects, and children with SGA have high levels of insulin resistance (12). This present study showed a statistically significant increase in HbA1c, fasting blood glucose, and fasting and sigma IRI in the OGTT compared with the pre-trial test. Sas et al. have reported that basal blood glucose levels are slightly increased, the basal and stimulated insulin levels during the OGTT are increased, and accordingly insulin resistance is increased in children with SGA short stature undergoing rhGH treatment. However, they did not find significant changes in glucose tolerance and reported that the HbA1c levels were within the reference range at all times (13). Saenger et al. summarized previous studies reporting the effects of rhGH treatment in patients with SGA short stature in 2007 (14). They concluded that rhGH treatment is unlikely to increase the risk of developing type 2 diabetes for the following reasons: with respect to the rhGH effects on glucose tolerance, there are no changes in glycated hemoglobin levels and insulin resistance before and after rhGH treatment; and although the fasting insulin concentrations do increase during rhGH treatment, they fall within the normal range after the completion of rhGH treatment. Horikawa et al. reported that they did not find any adverse effects on glucose metabolism in a clinical trial in Japanese children with SGA short stature (15). In this study, we also found that HbA1c, fasting blood glucose levels, IRI levels, and the sigma IRI of the OGTT were higher during treatment than before treatment. Although a considerable number of cases showed a shift from normal to borderline in the OGTT, no patients developed diabetes. The increase in HbA1c levels was also slight. Our findings are consistent with the reports by Horikawa et al. and Tanaka et al. who have also reported similar results for the effects of rhGH treatment in patients with SGA short stature in Japan (15, 16). Considering the present and previous results, it is assumed that rhGH treatment does not impose a particular risk for the development of type 2 diabetes, although rhGH treatment caused a slight increase in the glucose tolerance-related parameters based on insulin resistance. Given that the influence of rhGH treatment on glucose metabolism, even in GH deficiency short stature, is not fully understood, the administration of rhGH to patients with SGA short stature with normal GH secretion should be conducted in accordance with the guidelines and recommendations of the regulatory authorities while carefully observing the blood glucose, HbA1c, and urinary glucose levels.

In summary, the 24-mo 2-dose comparative study of rhGH treatment resulted in a higher growth-promoting effect in the high-dose group compared with the low-dose group. In addition, in the follow-up extension study of the low-dose group, a good growth-promoting effect was sustained in all the low-dose groups by maintaining or increasing the rhGH dose based on the effect of treatment in accordance with the guidelines. The questionnaire survey revealed that the score of items related to short stature improved after the 24-mo treatment. An analysis of the adverse events and adverse drug reactions did not reveal any differences between the different dose groups. The rhGH treatment showed statistically significant, but slight increases in glucose tolerance-related parameters based on insulin resistance.

On the basis of a recent European study of the long-term prognosis of patients treated with
rhGH, the regulatory authorities in Japan and other countries are urging compliance with the approved doses (17). Taking this into account, it is important to start and continue treatment of children with SGA short stature at an appropriate rhGH dosage regimen in accordance with the doses recommended in the guidelines.

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Conflict of Interests: The present study reports the results of clinical trials conducted by JCR Pharmaceuticals Co., Ltd. Hideaki Hirai is an employee of JCR Pharmaceuticals Co., Ltd. This study was conducted under the following structure:

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References

1. Albertsson-Wikland K, Karlberg J. Natural growth in children born small for gestational age with and without catch-up growth. *Acta Paediatr Suppl* 1994; 399: 64–70, discussion:71. [Medline]
2. Itabashi K, Mishina J, Tada H, Sakurai M, Nanri Y, Hirohata Y. Longitudinal follow-up of height up to five years of age in infants born preterm small for gestational age; comparison to full-term small for gestational age infants. Early Hum Dev 2007; 83: 327–333. [Medline] [CrossRef]

3. Hokken-Koelega AC, De Ridder MA, Lemmen RJ, Den Hartog H, De Muinck Keizer-Schrama SM, Drop SL. Children born small for gestational age: do they catch up? Pediatr Res 1995; 38: 267–271. [Medline] [CrossRef]

4. Tanaka T, Yokoya S, Nishi Y, Hasegawa Y, Yorifuji T, Fujieda K, et al. Guideline for growth hormone therapy in children with small-for-gestational-age short stature. J Jpn Pediatr Soc 2007; 111: 641–646 (in Japanese).

5. The Japanese Society for Pediatric Endocrinology. Practical approach to ensure appropriate growth hormone therapy of small-for-gestational-age short stature. Revised on Oct 4, 2010. (http://plaza.umin.ac.jp/~jspn/SGA.pdf) (in Japanese).

6. Tanaka T, Yokoya S, Seino Y, Togari H, Mishina J, Kappelgaard AM, et al. Long-term efficacy and safety of two doses of growth hormone in short Japanese children born small for gestational age. Horm Res Paediatr 2011; 76: 411–418. [Medline] [CrossRef]

7. Tanaka T, Yokoya S, Fujieda K, Seino Y, Tada H, Mishina J, et al. Efficacy and Safety of up to 8 years of long-term growth hormone treatment in short children born small for gestational age in Japan: analysis of the subpopulation according to the Japanese guideline. Clin Pediatr Endocrinol 2012; 21: 57–68. [Medline] [CrossRef]

8. Ito Y, Kato N, Tachibana K, Fujieda K. “Standard height table” and “Standard growth curve” version 2000 that conform with the height criteria adopted by the research project on treatment of specific pediatric chronic diseases. The Journal of Pediatric Practice 2005; 7: 1343–1351 (in Japanese).

9. Suwa S, Tachibana K. Standard growth charts for height and weight of Japanese children from Birth to 17 years based on a cross-sectional survey of national data. Clin Pediatr Endocrinol 1993; 2: 87–97. [CrossRef]

10. Murata M. Japanese specific bone age standard on the TW2. Clin Pediatric Endocrinol 1993; (suppl 3): 35–41. [CrossRef]

11. Osada H, Ogawa M, Tanaka T. Psychosocial aspect in short stature children - comparison with healthy children. Horumon To Rinsho 2007; 55: 67–71 (in Japanese).

12. Soto N, Bazaes RA, Peña V, Salazar T, Avila A, Iñiguez G, et al. Insulin sensitivity and secretion are related to catch-up growth in small-for-gestational-age infants at age 1 year: results from a prospective cohort. J Clin Endocrinol Metab 2003; 88: 3645–3650. [Medline] [CrossRef]

13. Sas T, Mulder P, Aanstoot HJ, Houdijk M, Jansen M, Reeser M, et al. Carbohydrate metabolism during long-term growth hormone treatment in children with short stature born small for gestational age. Clin Endocrinol (Oxf) 2001; 54: 243–251. [Medline] [CrossRef]

14. Saenger P, Czernichow P, Hughes I, Reiter EO. Small for gestational age: short stature and beyond. Endocr Rev 2007; 28: 219–251. [Medline] [CrossRef]

15. Horikawa R, Tanaka T, Nishinaga H, Ogawa Y, Yokoya S. The influence of a long-term growth hormone treatment on lipid and glucose metabolism: a randomized trial in short Japanese children born small for gestational age. Int J Pediatr Endocrinol 2016; 2016: 19. [Medline] [CrossRef]

16. Tanaka T, Yokoya S, Fujieda K, Seino K, Tada H, Mishina J. Efficacy and safety of long-term growth hormone therapy in Japanese children with small-for-gestational-age short stature (follow-up study) - review of cases that followed the treatment initiation standard as recommended in the guidelines in Japan. Horumon To Rinsho 2010; 58: 341–352 (in Japanese).

17. Carel JC, Ecosse E, Landier F, Meguellati-Hakkas D, Kagueidou F, Rey G, et al. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. J Clin Endocrinol Metab 2012; 97: 416–425. [Medline] [CrossRef]