

Original Article

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

Toshiaki Tanaka¹, Susumu Yokoya², Kenji Fujieda³, Yoshiki Seino⁴, Hiroshi Tada⁵,
Jun Mishina⁶, Susumu Saito⁷, Ami Takata⁷, and Nobuhiko Ohki⁷

¹Tanaka Growth Clinic, Tokyo, Japan

²Department of Medical Subspecialties, National Center for Child Health and Development, Tokyo, Japan

³Department of Pediatrics, Asahikawa Medical University, Hokkaido, Japan

⁴Osaka Koseinenkin Hospital, Osaka, Japan

⁵Toho University School of Medicine, Tokyo, Japan

⁶Sanchikai Medical Corporation, Kanagawa, Japan

⁷Pfizer Japan Inc., Tokyo, Japan

Abstract. The efficacy and safety of 8 yr of GH treatment was assessed in 44 Japanese children with small for gestational age (SGA) short stature who met the criteria for GH treatment initiation (height SD score (SDS) < -2.5 SD) of the Japanese guidelines. Height SDS in subjects improved throughout the study period, and average height SDS improved from -3.5 to -1.6 and from -3.4 to -1.9 in the 0.033/0.067 mg and 0.067/0.067 mg groups, respectively, after 8 yr of GH treatment. Delta height SD was approximately +2 after 4 yr of treatment, and Δ IGF-1 showed a significant positive correlation with Δ height SD after both 1 and 2 yr ($r = 0.415$ and 0.488 , respectively) of treatment. There was no correlation between the age at the start of treatment and age at onset of puberty, and the median age at the onset of puberty in the subjects was almost the same as that in healthy children. In conclusion, clinically significant improvements in the height SDS was confirmed in short children born SGA after 8 yr of GH treatment without any safety problems.

Key words: Genotropin[®], small for gestational age (SGA) clinical study, SGA short stature, GH treatment, puberty

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Correspondence: Dr. Toshiaki Tanaka, Tanaka Growth Clinic, 2-36-7 Yohga, Setagaya-ku, Tokyo 154-0097, Japan

E-mail: toshi_tnk@tanaka-growth-clinic.com

SS, AT and NO are employed by Pfizer Japan. AT is a statistician and was in charge of statistical analysis. TT, SY, KF, YS, HT, and JM, who are the advisors of this clinical study, reviewed the statistical analysis, discussion and conclusion. TT is responsible for this report.

Introduction

While approximately 90% of children born small for gestational age (SGA) have catch-up growth with a height SD score (SDS) of more than -2 by 2 yr of age, those in which catch-up growth does not occur within this first two years of life are defined as having SGA short stature. Most of the children with SGA short stature

remain short through to adulthood (1, 2), constituting about 20% of short adults (3). For this reason, GH treatment for children with SGA short stature was approved for use in 2001 in the USA, in 2003 in Europe, and in 2008 in Japan.

This clinical study was conducted for the approval of GH treatment for SGA short children with Genotropin[®]. In this clinical study of SGA short stature in Japan, the subjects were randomly assigned to two groups that received a different dose of GH (Genotropin[®]) treatment (0.033 mg/kg/d or 0.067 mg/kg/d). After treatment for one year, the dose was escalated to 0.067 mg/kg/d in the group receiving 0.033 mg/kg/d of GH (hereafter abbreviated as the 0.033/0.067 mg group), while children assigned to the group that received 0.067 mg/kg/d remained on the same dose (hereafter abbreviated as the 0.067/0.067 mg group).

Since we commenced this study before the Japanese guidelines were published, we initially conducted the study by applying a height SDS ≤ -2 as the criteria for initiating GH treatment, which is the same criterion used in other growth failure studies. However, when the Japanese guideline (4) for the treatment of SGA short stature was later published, and its criteria for GH treatment was stipulated as a height SDS of < -2.5 , based on the assumption that children with a height SDS of $+0.5$ may possibly catch up through puberty by adulthood even without GH treatment (1). Therefore, we extracted those subjects whose height SDS was < -2.5 .

We have previously reported (5) the efficacy and safety of up to 6 yr of long-term growth hormone treatment in a subpopulation of Japanese short children born SGA from the original study, who all met the criteria for GH treatment initiation according to the Japanese guidelines.

Here, we report the long-term efficacy and safety of GH treatment based on up to 8 yr of long-term data collected from the group of children with SGA short stature who had met

the criterion of a height SDS of < -2.5 as stipulated in the Japanese guideline for GH treatment. We also report the influence of GH treatment on the onset of puberty, and the correlation between the increase in IGF-1 levels and height SDS improvement in these children.

This study is an ongoing post-marketing clinical study, since the GH treatment for SGA short stature was approved in 2008.

Subjects and Methods

Of the subjects from a comparative study involving 2 different dose groups of GH treatment in children with SGA short stature (study number: 307-MET-0021-002, hereafter abbreviated as Study 002) and a subsequent long-term study (study number: GENASG-0021-007, hereafter abbreviated as Study 007) in those subjects who completed Study 002, efficacy and safety of up to 8 yr of long-term GH treatment were evaluated in the subpopulation of these subjects who met the criterion for GH treatment initiation according to the Japanese guideline (height SDS < -2.5).

This trial was performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from the subjects themselves or the subjects' parents/legal guardians.

The study designs of Study 002 and Study 007 are shown in Fig. 1. In Study 002, subjects were randomly assigned to one of two groups that received either 0.033 mg/kg/d or 0.067 mg/kg/d of GH. In Study 007, those subjects who were assigned to receive 0.033 mg/kg/d of GH in Study 002 had the dose escalated to 0.067 mg/kg/d (0.033/0.067 mg group), while those that received 0.067 mg/kg/d continued to be treated with the same dose (0.067/0.067 mg group) in general. While this is still an ongoing study, here we present the progress results for 8 yr of GH treatment.

Although the initial enrollment criterion for height SDS was ≤ -2.0 in Study 002, analyses for

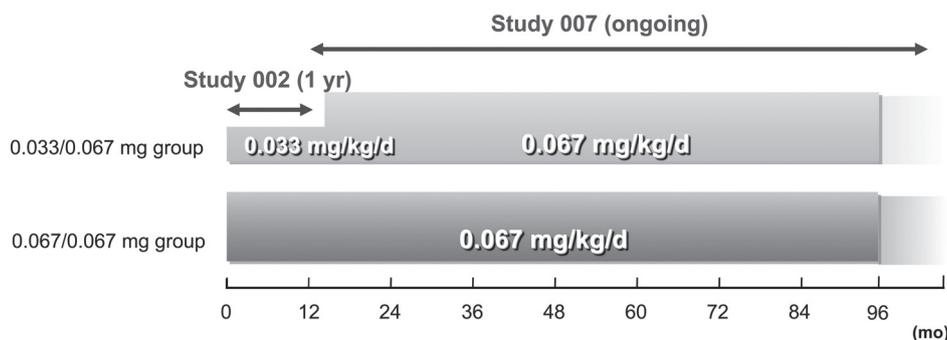


Fig. 1 Study designs of Study 002 and Study 007.

the current study were performed only on the subpopulation of children with SGA short stature who had a height SDS of <-2.5 at the time of enrollment in Study 002.

Main eligibility criteria other than height SDS in Study 002 were as follows:

- (1) Subjects with a birth weight and birth height below the 10th percentile for gestational age, and birth weight or birth height that was ≤ -2.0 SDS for gestational age
- (2) Chronological age: ≥ 3 and < 8 yr old for boys and ≥ 3 and < 7 yr old for girls
- (3) Height velocity SDS at 1 yr before the start of GH treatment: ≤ 0
- (4) Subjects with a peak GH level > 10 ng/mL in a GH stimulation test (excluding GRF and glucagon-propranolol provocation test)
- (5) Subjects who have not developed secondary sexual characteristics yet (Tanner Stage I)
- (6) Subjects whose height data from 1 yr prior to the start of GH treatment is available

In addition to the above criteria, subjects should not have a previous history of GH treatment in the two years prior to the study or receiving any hormone treatment that could affect growth. Furthermore, subjects with the following complications were excluded from the study: short stature due to endocrine disorder; abnormal chromosome or malformation syndrome (except Russell-Silver syndrome); skeletal diseases such as chondrodystrophy; subjects with a past treatment history of

radiotherapy or chemotherapy; subjects with serious heart, renal, or hepatic diseases; diabetic mellitus/abnormal glucose metabolism; serious chronic diseases; and subjects with malignant tumors.

Height velocity SDS, height SDS, and weight SDS were calculated using Japanese reference values by sex and age (6). The bone age of the TW2-RUS method (7) standardized for Japanese children was assessed by an independent medical specialist on XP radiographic films (copies) of the left hand of subjects whose names and study center names had been masked and randomly allocated. Parental-adjusted height SDS (PAH-SDS) was calculated using the formula: PAH-SDS = height SDS – target height SDS. Target height was calculated by using the formula reported by Ogata *et al* (8).

Endocrine tests (serum IGF-1, serum IGFBP-3, TSH, fT3, fT4, anti-hGH antibody), blood biochemistry tests [AST(GOT), ALT(GPT), γ -GTP, ALP, bone-type ALP, osteocalcin, total protein, BUN, creatinine, total cholesterol, Na, K, Cl, Ca, P, HbA_{1c}, fasting blood glucose], sex hormones [testosterone, FSH], and urinalysis (urinary GH), were all performed by Mitsubishi Chemical BCL Co., Ltd. (currently as Mitsubishi Chemical Medicine Corporation) as the laboratory for centralized measurement. IGF-1 SDS was calculated with Japanese reference values of the serum IGF-1 concentration in children by sex and age (9). In addition, the oral

Table 1 Clinical characteristics of the subjects at birth and start of GH treatment

	0.033/0.067 mg group		0.067/0.067 mg group	
Neonatal				
Male/Female	10/10	(20)	14/10	(24)
Birth length(cm)	38.9 ± 5.5	(20)	39.8 ± 5.9	(24)
Birth weight(g)	1559.3 ± 591.2	(20)	1704.7 ± 675.6	(24)
Gestational age (wk)	35.9 ± 3.4	(20)	37.0 ± 3.5	(24)
Initial dose				
Chronological age	5.1 ± 1.6	(20)	5.2 ± 1.3	(24)
Bone age	4.1 ± 1.8	(20)	4.5 ± 1.6	(23)
Height (cm)	91.5 ± 8.7	(20)	92.7 ± 7.2	(24)
Height SDS	-3.5 ± 0.6	(20)	-3.4 ± 0.8	(24)
PAH SDS	-3.4 ± 1.1	(20)	-3.0 ± 1.1	(24)
Growth rate (cm/yr)	5.2 ± 1.1	(20)	5.4 ± 1.3	(24)
Growth rate SDS	-2.1 ± 1.2	(20)	-1.6 ± 1.7	(24)
Weight (kg)	11.4 ± 2.5	(20)	11.4 ± 1.9	(24)
Weight SDS	-2.7 ± 0.7	(20)	-2.7 ± 0.6	(24)
Percent overweight (%)	-14.5 ± 8.8	(20)	-15.7 ± 7.3	(24)
Serum IGF-1 concentration (ng/mL)	126.4 ± 66.0	(20)	106.8 ± 40.6	(22)
Serum IGF-1 SDS	0.02 ± 1.43	(20)	-0.25 ± 1.10	(22)

Mean ± SD (n).

glucose tolerance test (OGTT) was performed at one-year intervals from the time when GH treatment was started.

The percent overweight was calculated with the following formula: (measured weight – standard weight) / standard weight × 100. The standard weight was calculated by the formula reported by Ito (10) using the subject's actual measured height.

Height velocity and height SDS were visualized using box-whisker plots to assess growth effects during 8 yr of GH treatment. Also, Δ height SDS was visualized using mean plots during 8 yr of GH treatment, and Δ height SDS after 1 yr of GH treatment was tested between the two groups by two-sided Wilcoxon rank-sum test at a significance level of 0.05. The correlation between Δ height SDS and Δ IGF-I SDS was assessed by Pearson's correlation coefficient, which was tested at a significance level of 0.05.

Results

Among the subjects treated in Study 007 (61 cases), 44 subjects met the criterion for GH treatment of the Japanese guideline (height SDS < -2.5), and all data from the 44 subjects who had been treated with GH for 8 yr (until March 31, 2011) were included in the analysis set.

Clinical characteristics of the subjects at birth and start of GH treatment are shown in Table 1. Demographic characteristics such as clinical characteristics at birth and clinical signs at the start of GH treatment were similar between the two treatment groups. Chronological age (mean ± SD) at the start of GH treatment was 5.1 ± 1.6 yr in the 0.033/0.067 mg group and 5.2 ± 1.3 yr in the 0.067/0.067 mg group. Meanwhile, height SDS (mean ± SD) at the start of GH treatment was -3.5 ± 0.6 in the 0.033/0.067 mg group and -3.4 ± 0.8 in the 0.067/0.067 mg group, with the mean PAH SDS below -3.0 in both groups. The mean serum IGF-1 concentration

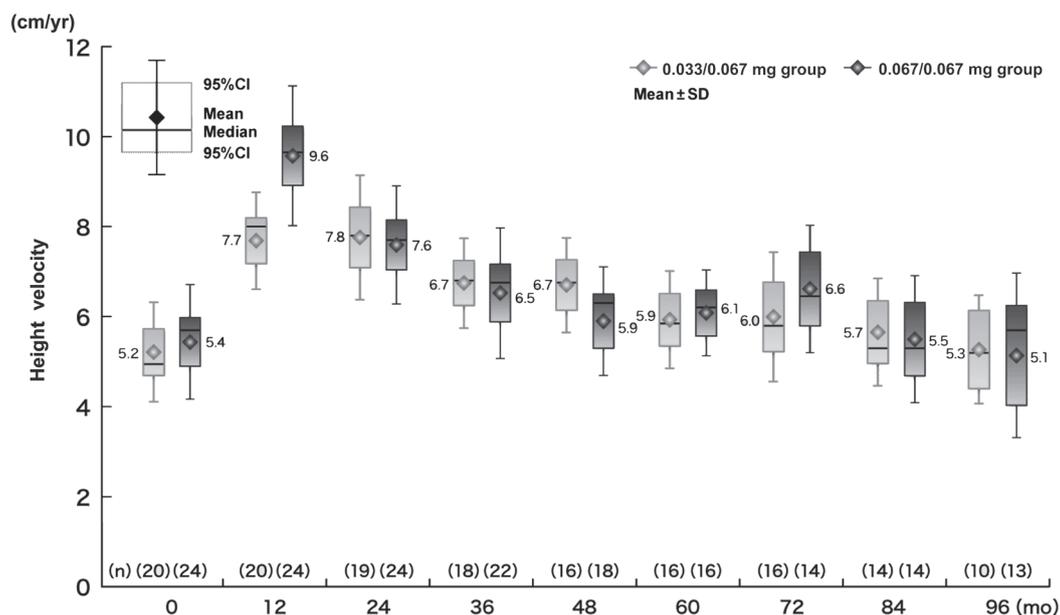


Fig. 2 Change in height velocity during 8 yr of GH treatment.

was about the same as the reference values by sex and age. The mean percent overweight was about -15% in both groups, with a trend for the children to be thin observed in both groups.

In this study, discontinuation of treatment was seen in 27 subjects (12 subjects in the 0.033/0.067 mg group and 15 subjects in the 0.067/0.067 mg group). The most frequent reason for discontinuation was the subject's retraction of consent (11 cases). Three subjects discontinued treatment as they had achieved a height SDS of 0 (in accordance with the discontinuation criteria of the protocol), while 6 subjects discontinued treatment as they had reached adult bone age (in accordance with the discontinuation criteria of the protocol). Other reasons for discontinuation were adverse drug reactions (jaw malformation), personal reasons, protocol deviation, and change in the course of the subject's management.

Adult heights of the above 6 subjects who reached adult bone age were 156.1–164.5 cm in 4 boys, and 139.3 and 138.3 cm in 2 girls.

Changes in the height velocity (cm/yr) are shown in Fig. 2. In both groups, height velocity increased remarkably 1 yr after the start of GH

treatment. Mean height velocity increased from 5.2 cm/yr at baseline to 7.7 cm/yr in the 0.033/0.067 mg group and from 5.4 cm/yr at baseline to 9.6 cm/yr in the 0.067/0.067 mg group, after 1 yr of GH treatment. Height velocity in the 0.033/0.067 mg group further increased to 7.8 cm/yr in the 2nd yr after escalation of the GH dose but then started to gradually decrease after 3 yr of treatment, while in the 0.067/0.067 mg group, a gradual decrease in the height velocity began to be observed after 2 yr of treatment.

Improvement of height SDS was observed throughout the study period (Fig. 3). Mean height SDS in the 0.033/0.067 mg group improved from -3.5 at baseline to -1.6 , and from -3.4 at baseline to -1.9 in the 0.067/0.067 mg group, after 8 yr of GH treatment.

The mean change in height SDS (Δ height SDS) from baseline after 8 yr of treatment was $+2.1$ in the 0.033/0.067 mg group and $+1.8$ in the 0.067/0.067 mg group (Fig. 4). Delta height SDS improved significantly after 1 yr in the 0.067/0.067 mg group compared with the 0.033/0.067 mg group ($p=0.001$). The increase in height SDS was maintained at around $+2$ from the 4th yr onwards.

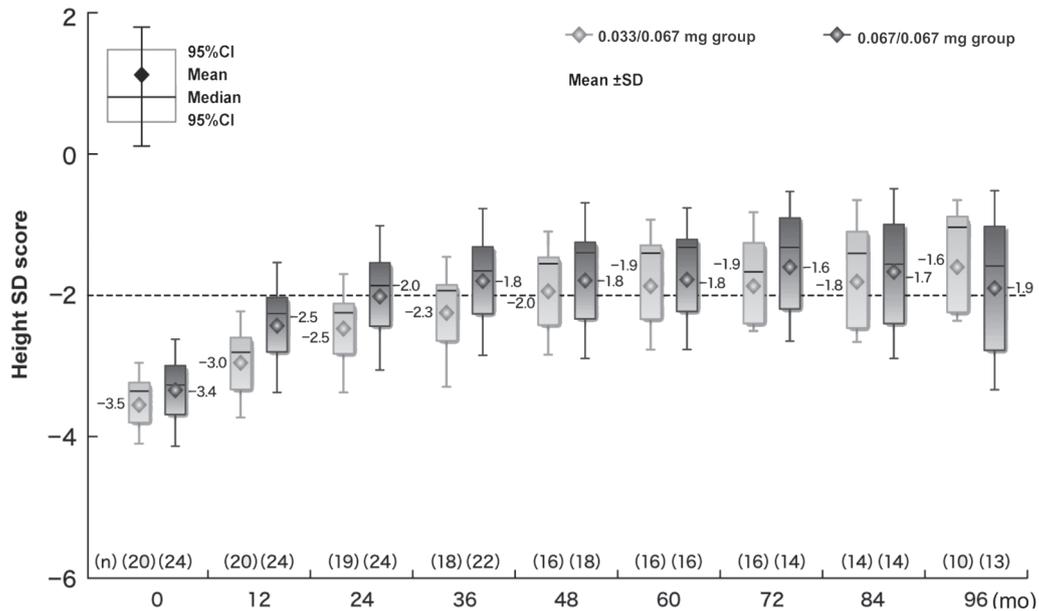


Fig. 3 Change in height SD score during 8 yr of GH treatment.

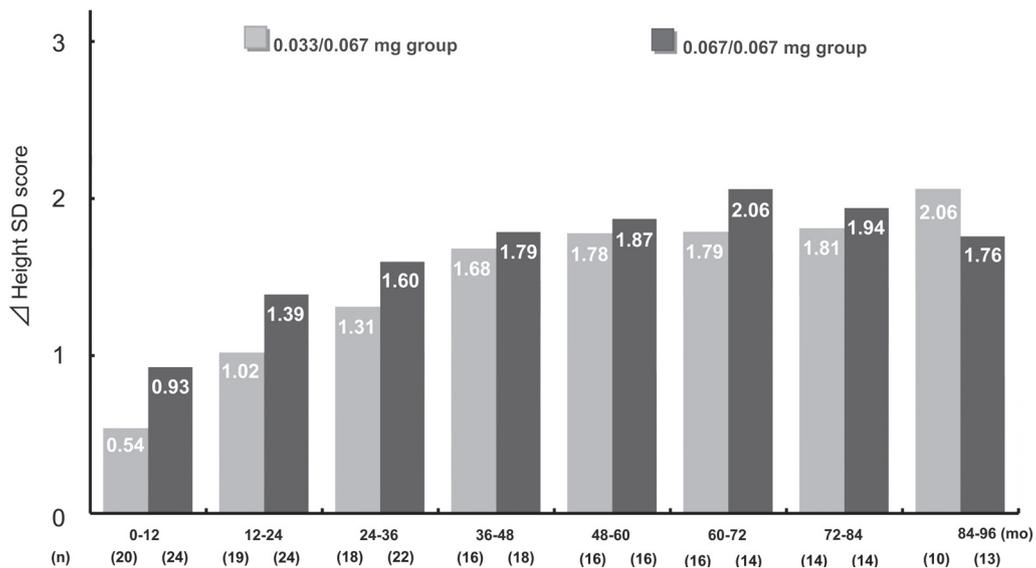


Fig. 4 Δ Height SD score during 8 yr of GH treatment.

The increases in IGF-1 SDS was significantly correlated with Δ height SDS at both 1 yr ($r=0.415$, $p=0.006$) and 2 yr ($r=0.488$, $p=0.001$) after the start of GH treatment (Fig. 5). There was a tendency for height gains to be greater when there were greater increases in IGF-1.

The change in distribution of subjects when categorized by 4 different ranges of height SDS, from the start of GH treatment to 6 yr after treatment, is shown in Fig. 6. While 50% of subjects in the 0.033/0.067mg group had catch-up growth with a height SDS above -2 after 3 yr

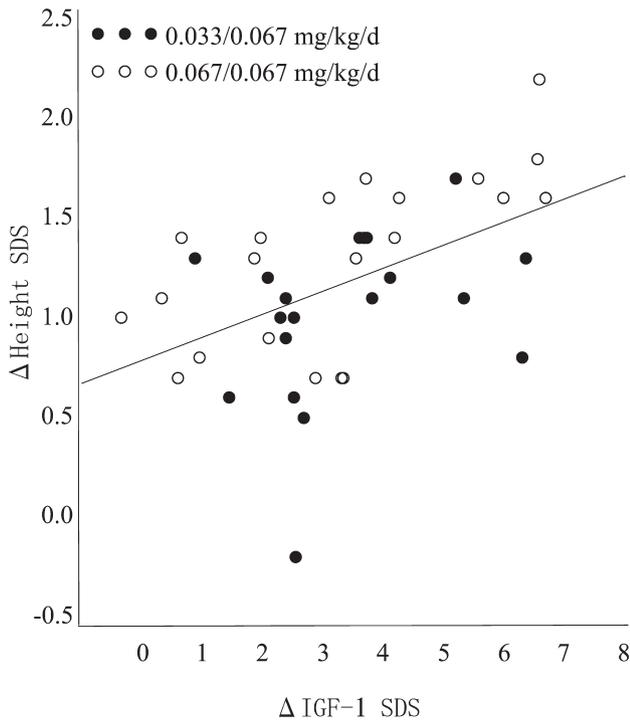


Fig. 5 Correlation between Δ IGF-1 SDS and Δ height SDS at 2 yr after the start of GH treatment (N=42). Pearson's correlation coefficient (r)=0.488, p =0.001.

of treatment, 50% of subjects in the 0.067/0.067 mg group reached a normal height (Δ height SDS $>$ -2) after 2 yr of treatment, 1 yr earlier than the 0.033/0.067 mg group. The normalization percentage of subjects (proportion of subjects with a height SDS over -2) after 6 yr of GH treatment was 62.5% in the 0.033/0.067 mg group and 78.6% in the 0.067/0.067 mg group.

We also observed annual average bone age changes (calculated as Δ bone age/ Δ chronological age) for eight years and found out that the average bone age changes were 0.5 to 0.6 during the first 12 mo, which means that the bone age changes were below chronological age changes. During the following months until year 8, the average bone age changes were between 0.8 and 1.5.

The list and percentage of (cumulative frequency) of subjects who developed pubertal change (Tanner Stage II) are shown in Table 2 and Fig. 7, respectively. During the study, development of secondary sexual characteristics was observed in 15 boys and 15 girls. The median age of onset of puberty was 11 yr and 5 mo in boys and 10 yr and 4 mo in girls.

One girl developed early puberty at 6 yr and

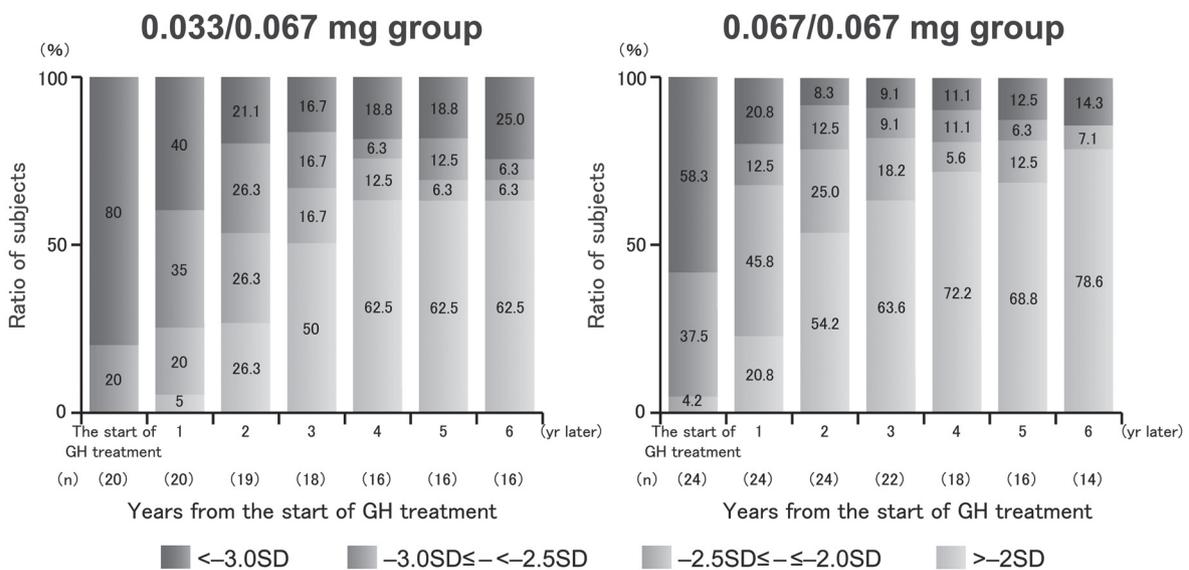


Fig. 6 Change in the percentage of the range of height SDS (over 6 yr).

Table 2 Clinical characteristics of the subjects at onset of puberty

Group	Initial dose (Age)	Onset of puberty			Duration of dosage (mo)
		Age	Height (cm)	Height SDS	
Male (n=15)					
0.033/0.067 mg	4 yr 10 mo	10 yr 5 mo	135.2	-0.5	66
	3 yr 3 mo	11 yr 3 mo	137.9	-0.8	96
	7 yr 9 mo	11 yr 5 mo	135.4	-1.3	45
	3 yr 7 mo	12 yr 0 mo	137.2	-1.5	102
	7 yr 10 mo	12 yr 3 mo	136.5	-1.7	51
	7 yr 6 mo	12 yr 6 mo	142.6	-1.1	60
0.067/0.067 mg	4 yr 7 mo	10 yr 4 mo	131.2	-1.1	69
	7 yr 6 mo	10 yr 6 mo	126.4	-2.0	36
	3 yr 8 mo	10 yr 8 mo	127.1	-2.0	84
	6 yr 1 mo	10 yr 10 mo	134.3	-1.0	57
	7 yr 5 mo	11 yr 1 mo	136.1	-0.9	45
	5 yr 5 mo	11 yr 5 mo	139.4	-0.7	72
	4 yr 0 mo	12 yr 0 mo	143.0	-0.7	96
	7 yr 7 mo	12 yr 3 mo	121.4	-3.7	57
3 yr 8 mo	12 yr 8 mo	146.8	-0.7	108	
Female (n=15)					
0.033/0.067 mg	3 yr 2 mo	6 yr 2 mo	105.8	-1.7	36
	6 yr 2 mo	9 yr 6 mo	121.5	-2.0	39
	6 yr 11 mo	9 yr 11 mo	119.1	-2.7	36
	4 yr 10 mo	10 yr 10 mo	133.6	-1.2	72
	5 yr 6 mo	11 yr 0 mo	134.9	-1.2	66
	3 yr 6 mo	11 yr 0 mo	123.8	-2.9	90
0.067/0.067 mg	5 yr 3 mo	7 yr 6 mo	109.3	-2.5	27
	4 yr 11 mo	8 yr 11 mo	114.2	-2.8	48
	4 yr 6 mo	9 yr 0 mo	130.0	-0.1	39
	4 yr 4 mo	10 yr 0 mo	138.2	0.3	48
	5 yr 5 mo	10 yr 4 mo	129.1	-1.4	60
	4 yr 8 mo	10 yr 5 mo	129.4	-1.5	69
	6 yr 8 mo	10 yr 8 mo	128.4	-1.8	48
	4 yr 10 mo	10 yr 10 mo	116.8	-3.8	72
3 yr 8 mo	11 yr 2 mo	132.1	-1.8	90	

2 mo, and she was diagnosed as having precocious puberty, while all other subjects began puberty within the normal range for Japanese children. There was no correlation between the age at the start of GH treatment and the onset of puberty ($r=0.104$ in boys and $r=0.191$ in girls). The average height at onset of puberty was 135.4 ± 6.7 cm in boys and 124.4 ± 9.7 cm in girls.

During 8 yr of treatment, adverse events

were observed in 43 out of 44 subjects (97.7%). Major adverse events included upper respiratory tract infections in 39 subjects (88.6%), influenza-like symptoms in 27 subjects (61.4%), gastroenteritis in 22 subjects (50.0%), otitis media in 20 subjects (45.5%), bronchitis in 16 subjects (36.4%), rhinitis in 15 subjects (34.1%), and conjunctivitis in 15 subjects (34.1%). Adverse events for which causality with GH could not be

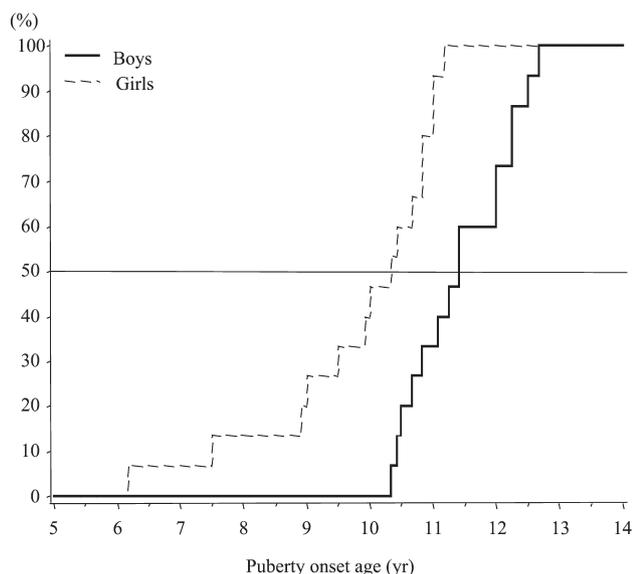


Fig. 7 Percentage (cumulative frequency) of subjects who enter puberty.

ruled out included two cases of adenoid vegetations and one case of jaw malformation, and in the latter case (a girl in the 0.067/0.067 mg group), the treatment was discontinued permanently.

Influence on glucose tolerance was assessed by the OGTT once a year. No subject showed a diabetic pattern of glucose in the OGTT, and the level of HbA_{1c} was within the normal range throughout the 8 yr period in all subjects.

Discussion

The mean height SDS of the 0.033/0.067 mg group improved from -3.5 at baseline to -1.6 after 8 yr of treatment, while the 0.067/0.067 mg group similarly improved from -3.4 to -1.9 . However, while the mean height SDS increased from -3.5 at the start of treatment to -1.8 after 5 yr of treatment in the 0.033/0.067 mg group and from -3.4 to -1.8 after 4 yr of treatment in the 0.067/0.067 mg group, not much further improvement was seen in both groups after these respective times. These results indicate that even with the highest dose of GH treatment for SGA

short stature, the effective time for catch-up growth is only about 4–5 yr. However, compared with the maximum catch-up period of 2–3 yr in GH deficiency (GHD) patients, the present regimen for SGA showed longer catch-up and greater improvement. Meanwhile, the currently approved therapeutic dose of GH is 0.23 mg/kg/wk as the starting dose, and if this dose is not effective, then it can be increased to 0.47 mg/kg/wk. Compared with the 0.033/0.067 mg group, therefore, the approved regimen may be less effective in improving height SDS.

It is a new finding that improvements in height SDS are significantly positively correlated with changes in IGF-1 SDS, and this finding suggests that IGF-1 may directly promote growth as a GH-dependent growth factor. This finding also suggests the usefulness of monitoring IGF-1 when trying to determine the therapeutic dose of GH. It is also consistent with a study that involved GH treatment in GHD short children in which Cohen *et al.* (11) adjusted the dose of GH based on IGF-1 levels and demonstrated that higher IGF-1 levels promoted greater growth effects. Meanwhile, increases in the percentage of children with normalized height were not observed after the 4th yr of treatment. However, it is difficult to evaluate the effects using height SDS after 4–5 yr, since subjects begin to reach the age for puberty. While no consensus has been established on how to evaluate the effects of GH treatment during puberty, parameters to be evaluated are the age at onset of puberty, height at onset of puberty and height gains during puberty.

Since the age at onset of puberty was found to be significantly correlated with the age when GH treatment was started in GHD (12), it was suggested that GH treatment may accelerate the onset of puberty. However, no such correlation was observed in this study involving GH treatment for children with SGA short stature. Although early puberty was noticed in one girl, the median age at onset of puberty was 11 yr and 5 mo in boys and 10 yr and 4 mo in girls,

both of which were similar to those of healthy children. However, it is known that short stature children in general have delayed onset of puberty, and this subsequently results in a more apparent improvement in the adult height SDS compared with the pre-puberty SD score (13). Similarly, growth developmental data in children with untreated SGA short stature in Sweden also show more improvement in adult height SDS, by approximately +0.5, compared with pre-puberty values (1). Therefore, it is thought that the mean age at onset of puberty in children with SGA short stature is higher compared with healthy children. Development of precocious puberty in one girl may be the result of a possible acceleration of the onset of puberty due to high-dose GH treatment.

One of the objectives of GH treatment in children with short stature is to reduce the psychosocial problems associated with short stature by inducing catch up to normal height early, and to improve social adaptation through the normalization of their adult height. The percentage of children with normal stature exceeded 50% after 3 and 2 yr of treatment in the 0.033/0.067 mg and 0.067/0.067 mg groups, respectively. This represents a remarkable therapeutic efficacy of the present GH treatment, and it can be said that one of objectives of GH treatment has been achieved. Practically, improvements in QOL by GH treatment in children with SGA short stature have been reported previously (14–16). Excellent effects on adult height were observed by van Pareren *et al.* (17), who reported a mean adult height SDS of -1.1 in the 0.033 mg/kg/d group and -0.9 in the 0.067 mg/kg/d group and 85% of subjects achieved normal adult height. However, there are no complete reports in Japan on adult height after GH treatment for SGA short stature. In this study, while 6 subjects (4 boys and 2 girls) reached the bone age of an adult and were thus considered to have achieved adult stature, the statures of 2 out of the 4 boys and the 2 girls were still less than the normal adult height. The

Japanese criteria for GH treatment initiation is a height SDS of ≤ -2.5 , and children who meet this criteria are not expected to reach normal adult height without any treatment even if onset of puberty is delayed. Therefore, the achievement of a normal adult height itself shows a positive therapeutic effect. While further investigations are required with a larger number of subjects, many subjects in this study achieved normal stature, which suggests that there is a high possibility of achieving normal stature if there is no early onset of puberty.

A stature higher than -2 SD is academically defined as normal stature, with the height at -2 SD being 159.2 cm in males and 147.4 cm in females. However, clinically the minimum height that children suffering from short stature and their parents desire as the final adult height is typically 160 cm for males and 150 cm for females. These heights correspond to -1.86 SD for males and -1.53 SD for females, and are higher than the minimum limits of academically defined normal ranges, especially for females. Since there is a strong positive correlation between the height at onset of puberty and the adult height, it is essential for the child to have a sufficient height by the time of onset of puberty if they want to achieve the desired adult height. The height at the onset of puberty of healthy children is approximately 145 cm in boys (18) and 135 cm in girls (19), whereas the height at the onset of puberty in children with SGA short stature is 5–10 cm less than that of healthy children. Adult height has the strongest positive correlation with height at onset of puberty among clinical characteristics until onset of puberty. Analysis in short children demonstrated that those boys and girls who are shorter than 135 and 132.5 cm, respectively, at the onset of puberty will have difficulty achieving adult heights of more than 160 and 150 cm, respectively (20). We have advocated the naming of these children as “early puberty for height” and recognition of these children as a group with a high risk of short adult stature. In this study, for example, 5 out of 15

boys and 11 out of 15 girls had early puberty for height, and it is thought that it will be unlikely for the adult stature of these boys and girls to ever exceed 160 and 150 cm, respectively.

Incidental infections not related to GH treatment were observed as the main adverse events. One case of jaw malformation due to high-dose GH treatment was observed, and GH treatment in this subject was permanently discontinued.

Conclusion

The growth promoting effects of growth hormone in short children born SGA were confirmed in this clinical study of up to 8 yr of long-term GH treatment. Height SDS of subjects improved throughout the study period, and the increase in height SDS was approximately +2 after 4 yr of treatment.

Delta IGF-1 SDS was positively correlated with Δ height SDS, and so it is suggested that monitoring of IGF-1 levels may be meaningful when determining the GH dose.

Many children demonstrated catch-up growth to a normal height, which suggests a high possibility for these children to achieve normal adult stature.

There was no correlation between the chronological age at the start of GH treatment and the onset of puberty, and the time at the onset of puberty was almost the same between healthy children and children with SGA short stature. However, since it is suggested that the onset of puberty in untreated short children born SGA is delayed, there is still some possibility that the high-dose GH treatment might induce puberty earlier in children with SGA short stature.

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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 Scand* 1994;399(Suppl):64–70.
2. Karlberg J, Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. *Pediatr Res* 1995;38:733–9.
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;38:267–71.
4. The Japanese Society for Pediatric Endocrinology, Japan Society for Premature and Newborn Medicine. Guideline for GH treatment in SGA short children. *Nihon Shonika Gakkai Zasshi* 2007;111:641–6 (in Japanese).
5. Tanaka T, Yokoya S, Fujieda K, Seino Y, Tada H, Mishina J. Efficacy and safety of long-term growth hormone treatment up to 7 years in children born small for gestational age in Japan: analysis of subpopulation who meet with the

- criteria for GH treatment initiation of the Japanese guideline. *Horumon To Rinsho* 2010;58:341–52 (in Japanese).
6. 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.
 7. Murata M, et al. Atlas of Japanese standard skeletal maturation – using the TW2 method –. Tokyo: Kanehara & Co., Ltd.; 1993.
 8. Ogata T, Tanaka T, Kagami M. Target height and target range for Japanese children: revisited. *Clin Pediatr Endocrinol* 2007;16:85–7.
 9. Shimatsu A, Fujieda K, Haniu K, Tanaka T, Yokoya S, Miyachi Y, et al. Clinical evaluation of serum IGF-I, IGF-II and IGF-BP-3 measured by IRMA kits in childhood. *Horumon To Rinsho* 1996;44:1129–38 (in Japanese).
 10. Ito Y. 1. Commentary: Explanation of standard growth curve and disease-specific growth curve, explanation of obesity assessment curve. In: Fujieda K, editor. *Revelations of the growth curve: Pediatric diseases causing growth disturbance – cases and explanations –*. 1st ed. Tokyo: Shindan-to-chiryō-sha Co., Ltd; 2005. p.39–43.
 11. Cohen P, Rogol AS, Howard CP, Bright GM, Kappelgaard AM, Rosenfeld RG. Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study. *J Clin Endocrinol Metab* 2007;92:2480–6.
 12. Hibi I, Tanaka T. Final height of patients with idiopathic growth hormone deficiency after long-term growth hormone treatment. *Acta Endocrinol* 1989;120:409–15.
 13. Komatsu K, Okamura T, Takada G, Miyashita M, Ohno T, Tanaka T. Analysis of natural growth of children with short stature at prepuberty of at final height i. follow-up of healthy children at Akita prefecture. *Nihon Shonika Gakkai Zasshi* 1997;101:610–6 (in Japanese).
 14. Osada H, Takahashi R, Tanaka T. Psychosocial evaluation of growth hormone (GH) treatment in short children born small for gestational age. *The Journal of Child Health* 2009;68:240–7 (in Japanese).
 15. Osada H, Tanaka T, Fujieda K, Yokoya S, Seino Y, Togari H, et al. Comparison of QOL in SGA children with that in normal children and the change in QOL after growth hormone treatment for SGA children. *The Journal of Child Health* 2009;68:350–8 (in Japanese).
 16. Takahashi R, Osada H, Yokoya S, Itabashi K, Seino Y, Tanaka T. Assessment of psychological and social features of successful growth hormone treatment in SGA short stature children. *J Jpn Assoc Hum Auxol* 2011;17:77–82.
 17. van Pareren Y, Mulder P, Houdijk M, Jansen M, Reeser M, Hokken-Koelega A. Effect of discontinuation of growth hormone treatment on risk factors for cardiovascular disease in adolescents born small for gestational age. *J Clin Endocrinol Metab* 2003;88:347–53.
 18. Fujieda K, Matsuura N. Growth and maturation in the male genitalia from birth to adolescence. I. Change of testicular volume. *Acta Paediatr Jpn* 1987;29:214–9.
 19. Tanaka T, Imai T. The standard of breast development in normal girls: Diagnostic criteria for precocious puberty. *The Journal of Child Health* 2005;64:33–8 (in Japanese).
 20. Tanaka T, Naiki Y, Horikawa R. Clinical factors related to the short adult height: early puberty for height. *J Jpn Assoc Hum Auxol* 2011;17:17–23.