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CLINICAL STUDY

An individualized GH dose regimen for long-term GH treatment in Japanese patients with adult GH deficiency

Kazuo Chihara[1], Ekaterina Koledova[2], Akira Shimatsu[3], Yuzuru Kato[4], Hitoshi Kohno[5], Toshiaki Tanaka[6], Akira Teramoto[7], Peter C Bates[8] and Andrea F Attanasio[9]

[1]Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine, Kobe, Japan [2]Eli Lilly Japan K.K., Kobe, Japan [3]Clinical Research Center for Endocrine and Metabolic Disease, Kyoto Medical Center, Kyoto, Japan [4]Division of Endocrinology, Metabolism, Hematology and Oncology, Shimane University, Izumo, Japan [5]Department of Endocrinology and Metabolism, Fukuoka Children's Hospital, Fukuoka, Japan [6]Division of Endocrinology and Metabolism, National Center for Child Health and Development, Tokyo, Japan [7]Department of Neurosurgery, Nippon Medical School, Tokyo, Japan [8]Cambridge Medical Writing Services, Ickleton, Cambridge CB10 1SH, UK [9]Cascina del Rosone, Agliano Terme, Italy

(Correspondence should be addressed to K Chihara, Division of Endocrinology/Metabolism, Neurology and Hematology/Oncology, Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan; Email: chiharak@med.kobe-u.ac.jp)

Abstract

Objectives: To investigate the effects of growth hormone (GH) treatment, using a dose-adjustment regimen based on serum insulin-like growth factor (IGF)-I concentrations, in adult Japanese hypopituitary patients with GH deficiency.

Study design: Japanese patients who had initially been administered GH ($n = 31$) or placebo ($n = 28$) in a 24-week double-blind study received individualized GH treatment in an open-label study for 48 weeks. Body composition from dual-energy X-ray absorptiometry (DXA) and serum IGF-I, IGF-binding protein 3 (IGFBP-3) and lipid levels were determined centrally.

Results: Significant increases in lean body mass (4.5%) and decreases in fat mass (−10.5%) were observed in the group that received individualized GH doses in the present open-label study following placebo in the double-blind study. This was comparable with the changes observed in these parameters (4.7 and −9.2%, respectively) with fixed-dose GH treatment in the double-blind study; this latter group maintained these improvements throughout the open-label study. Individualized dose adjustment allowed for more moderate dose increases than the fixed-dose titration method. Individualized dosing also resulted in a lower mean dose for adult-onset compared with childhood-onset GH-deficient patients (0.032 ± 0.019 versus 0.061 ± 0.023 mg/kg per week for patients treated with GH for 48 weeks in the open-label study following placebo in the double-blind study). Dosing patterns in the two groups were paralleled by the changes in IGF-I and IGFBP-3. The incidence of oedema and cases with high IGF-I level were less frequent under the IGF-I controlled regimen compared with those during the fixed-dose titration method.

Conclusion: Individualized GH administration based on IGF-I levels was safe and effective. This regimen demonstrated differences in dose requirements between adult- and childhood-onset patients. An individualized dose regimen is recommended in adult Japanese GH-deficient patients.

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Introduction

Growth hormone (GH) is not only essential for growth in childhood but is also necessary in adults for normal metabolic regulation. GH replacement for adult patients with hypopituitarism was introduced into clinical practice in Europe and the USA almost a decade ago. Treatment modalities, such as GH dose, as well as efficacy and safety results during treatment and follow-up, have become established with experience (1–3). In Japan, the adult GH-deficiency (GHD) indication has not yet been approved but the existence of adult GHD syndrome in Japanese subjects has been demonstrated. At present, long-term data on efficacy and safety of GH replacement in adult Japanese patients is lacking.

In a recent report, we demonstrated the short-term efficacy and safety of GH treatment in 64 Japanese adult GHD patients in a placebo-controlled, double-blind study (4). In that study, adult patients with adult-onset (AO) or childhood-onset (CO) GHD were administered GH for a period of 24 weeks by an escalating, fixed-dose method culminating with 0.084 mg/kg per week (12 μg/kg per day) administered subcutaneously to all GH-treated patients. The GH treatment

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effects on body composition and lipids were significant compared with placebo and were qualitatively and quantitatively comparable with those seen in Caucasians using the same GH dose.

In the present study, which was an extension of the initial study, GH was continuously administered to all patients for 48 weeks. The primary objectives of this report were to evaluate the efficacy and safety of a GH dose-adjustment method based on insulin-like growth factor (IGF)-I concentrations for individual patients. Efficacy was evaluated from changes for patients starting individualized GH treatment and against changes observed previously with a fixed GH dose (4).

Patients and methods

This was a 48-week open-label study of GH treatment in Japanese adult GHD patients who had previously taken part in a 24-week placebo-controlled, double-blind study in 25 Japanese study centres (4). All patients gave informed consent and the study was performed with appropriate ethical approval according to the Declaration of Helsinki. In the double-blind study, 64 Japanese patients, with AO (mean age±S.D., 50.8±9.7 years) or CO (age, 28.8±7.3 years) GHD, were enrolled. Details of entry criteria for patients enrolled in the study have been described previously (4). All patients had a peak GH value of less than 3 μg/l during a standard stimulation test (insulin, arginine or glucagon) and any patients with malignancy, diabetes or hypertension were excluded. Of these patients, 33 were treated with GH in an escalating fixed-dose regimen and 31 received placebo during the double-blind study. At the end of this 24-week study, 31 patients who completed the active treatment (GH/GH group) and 28 patients who completed the placebo treatment in the double blind-phase (PL/GH group), entered an open-label 48-week GH dose-adjustment phase (Fig. 1). A total of five subjects had discontinued prior to 24 weeks of treatment in the double-blind study.

Patients were administered recombinant human GH (Humatrope; Eli Lilly and Company, Indianapolis, IN, USA) using cartridge pens. At the beginning of the open-label study, all patients, including those who had been given a fixed GH dose during the double-blind study, received a GH dose of 0.021 mg/kg per week for 8 weeks. Thereafter, the dose level was adjusted for each individual to between 0.021 and 0.084 mg/kg per week according to the serum IGF-I level measured during the previous visit, taking into account any side effects of GH treatment. This dose adjustment, tailored to the features of individual patients, was based on the Growth Hormone Research Society Consensus Guidelines (1) where the serum IGF-I level was maintained at between −1.96 S.D. and +1.96 S.D. (the normal range of IGF-I level by gender and age (5)).

During the open-label study, patient visits were scheduled every 4 weeks for the first 24 weeks followed by two 12-week intervals at 36 and 48 weeks. Measurements of IGF-I for dose adjustment, IGF-binding protein 3 (IGFBP-3) and other laboratory determinations were performed at the scheduled visits. At weeks 0, 24 and 48 of the open-label study, lean body mass (LBM) and fat mass were measured by

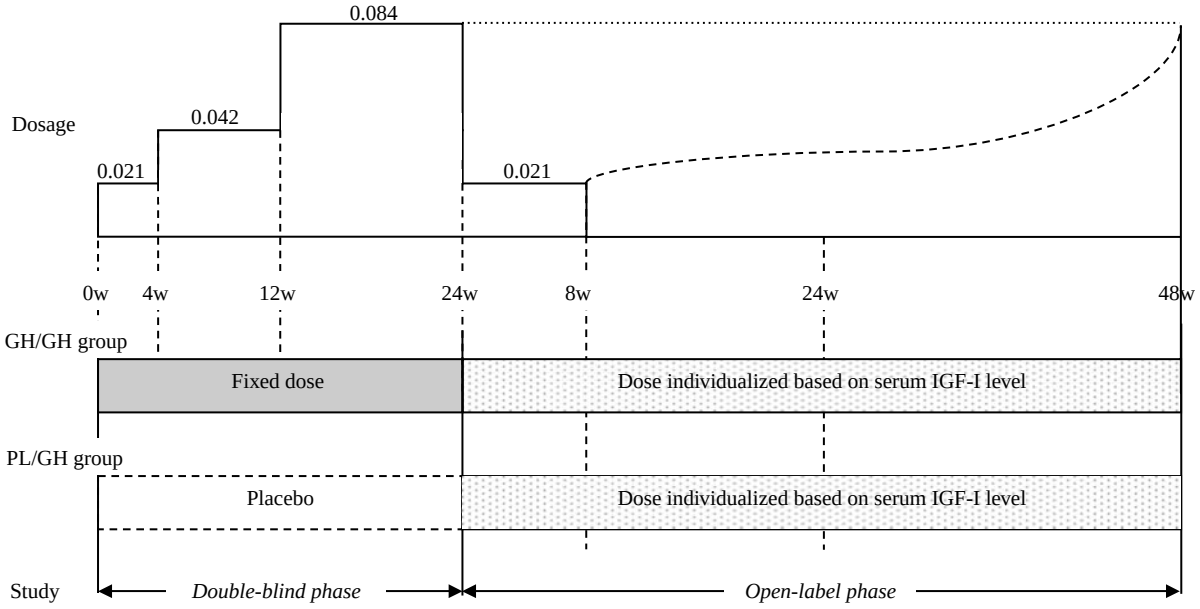

Figure 1 Dosing (mg/kg per week) and nomenclature for double-blind and open-label studies of GH administration to Japanese adult GHD patients.

Table 1 Baseline characteristics of Japanese adult GHD patients at the start of the open-label, individualized dose-adjustment study.

	PL/GH ($n = 28$)	**GH/GH** ($n = 31$)
Age (mean±S.D.; years)	39.6±13.7	36.2±13.3
Gender (male/female)	14/14	15/16
Onset (AO/CO)	11/17	12/19
Body weight (mean±S.D.; kg)	60.6±13.8	66.4±16.0
Body mass index (mean±S.D.; kg/m^2)	22.9±3.6	24.8±4.8
LBM (mean±S.D.; kg)	38.6±9.7	42.2±9.6
Fat mass (mean±S.D.; kg)	19.0±5.1	20.8±8.6
IGF-I (mean±S.D.; ng/ml)	61±39	243±114
IGF-I SDS (mean±S.D.)	−2.33±1.42	0.82±2.28
IGFBP-3 (mean±S.D.; μg/ml)	1.9±1.0	3.3±1.0
IGFBP-3 SDS (mean±S.D.)	−3.90±3.61	−0.17±2.42

dual-energy X-ray absorptiometry (DXA) in each investigative centre and evaluated centrally (Department of Radiology, Kawasaki Medical School, Kurashiki City, Okayama, Japan). Serum IGF-I and IGFBP-3, triglycerides, total cholesterol and low-density lipoprotein (LDL)-cholesterol concentrations were measured centrally (BML Inc., Shibuya-ku, Tokyo, Japan) using standard immunoradiometric assays for IGF-I and IGFBP-3 and enzymatic methods for cholesterol concentrations.

Safety was assessed by treatment-emergent adverse events (coded according to MedDRA, version 5.1) and by evaluation of laboratory test values and blood pressure. Laboratory determinations were performed centrally and included measurements of thyroid hormones and glycosylated haemoglobin (HbA1c) concentrations.

SD scores (SDSs) for serum IGF-I and IGFBP-3 concentrations were calculated by comparison to age- and gender-matched subjects from a healthy Japanese reference population (5). Cholesterol concentrations were originally determined in mg/dl with the assay kit; the conversion factor for mM is 0.02586 and in-text values have been converted and are shown in parentheses for reference. All results were analysed on an intent-to-treat basis and assessed at a two-tailed significance level of 5%. For all parameters, the baseline used to assess changes during the open-label study was the value observed at the end of the double-blind study. Changes in the open-label study were evaluated using last observation carried forward for all patients who started the open-label study, except for GH dose, IGF-I and IGFBP-3 values when only observed values were assessed. Differences between baseline and the end of study for body composition and lipid parameters were assessed by paired *t*-tests or Wilcoxon signed rank tests. All statistical analyses used SAS version 8.2 (SAS Institute, Cary, NC, USA).

Results

Baseline data

The baseline characteristics of the patients at the start of the open-label study are given in Table 1. The mean ages and numbers of male and female and AO and CO patients were similar in the GH/GH and PL/GH groups. The baseline characteristics of the PL/GH group at the beginning of the open-label study were similar to those reported for the start of the double-blind study (4). IGF-I and IGFBP-3 concentrations were below normal in the PL/GH group; in contrast, the IGF-I and IGFBP-3 concentrations and SDS values were improved in the GH/GH group at baseline of the open-label study following treatment in the double-blind study.

GH dose adjustment and IGF-I response

The time course of dose adjustments is given in Table 2 by GHD onset group. The starting dose was 0.021 mg/kg per week (3 μg/kg per day) and constant in both treatment groups for the first 8 weeks. In the subsequent dose-adjustment period the mean doses increased until week 24 and then stabilized through to week 48. Similar mean doses were being administered to the PL/GH (0.049±0.026 mg/kg per week) and the GH/GH (0.05±0.024 mg/kg per week) groups overall at the end of the open-label study. The mean doses in both groups were lower at the end of the open-label study than that being administered to the GH/GH group at the end of the escalating fixed-dose, double-blind study (0.078±0.015 mg/kg per week). The final dose adjusted according to IGF-I levels was lower in patients with AO

Table 2 Time course of GH dose in adult Japanese patients with AO or CO GHD in the individualized-dose (open-label) study (mean±S.D. (*n*)).

	Dose (mg/kg per week)			
	PL/GH		GH/GH	
Week in study	AO	CO	AO	CO
Week 8	0.021±0.001 (11)	0.021±0.001 (17)	0.021±0.001 (12)	0.021±0.001 (19)
Week 16	0.029±0.019 (11)	0.045±0.018 (17)	0.028±0.012 (12)	0.046±0.018 (18)
Week 24	0.034±0.015 (10)	0.058±0.022 (17)	0.041±0.025 (11)	0.059±0.021 (18)
Week 36	0.034±0.02 (11)	0.059±0.023 (17)	0.036±0.025 (12)	0.058±0.02 (18)
Week 48	0.032±0.019 (11)	0.061±0.023 (16)	0.035±0.025 (12)	0.059±0.019 (18)

compared with CO GHD in both the PL/GH (0.032±0.019 versus 0.061±0.023 mg/kg per week) and GH/GH groups (0.035±0.025 versus 0.059±0.019 mg/kg per week). The maximum and minimum doses for AO and CO patients at the end of the open-label study, in both the PL/GH (min–max, AO, 0.02–0.084 mg/kg per week; CO, 0.021–0.084 mg/kg per week) and GH/GH (AO, 0.01–0.085 mg/kg per week; CO, 0.032–0.085 mg/kg per week) groups in this IGF-I-controlled regimen, illustrate the wide range necessary for individual optimal doses.

The dosing patterns in the two groups were paralleled by the changes in IGF-I SDS and mean values within the normal range were achieved by both the PL/GH (0.38±1.67) and GH/GH (0.51±1.25) groups (Fig. 2, top panel). Overall, the mean IGF-I SDS values in the GH/GH group were similar to those observed at the endpoint of the escalating fixed-dose, double-blind study. In both treatment groups, IGF-I SDS at the end of the open-label study was consistently higher for AO than for CO patients (AO PL/GH, 1.51±1.11; CO PL/GH, −0.39±1.56; AO GH/GH, 0.86±1.28; CO GH/GH, 0.28±1.21). The introduction of the individualized dose-adjustment regimen eliminated excessively high values of IGF-I SDS seen in the GH/GH group in the double-blind study. The GH/GH group had IGF-I SDS above normal in six subjects (maximum 6.81) after the double-blind study and this declined to three subjects at the end of the open-label study (maximum, 2.82). IGF-I SDS was above normal in three subjects in the PL/GH group (maximum, 4.23) after 48 weeks of GH treatment. The IGFBP-3 SDS values during the open-label study (Fig. 2, bottom panel) reflected the changes in IGF-I and the mean values were within the normal range throughout GH treatment.

Efficacy

The overall increases in LBM and decreases in fat mass during the fixed-dose regimen and individualized-dose regimen are summarized in Table 3. There was no significant change in mean LBM or fat mass when the PL/GH group was treated with placebo in the double-blind study. In this group, the mean percentage increases in LBM and mean percentage decreases in fat

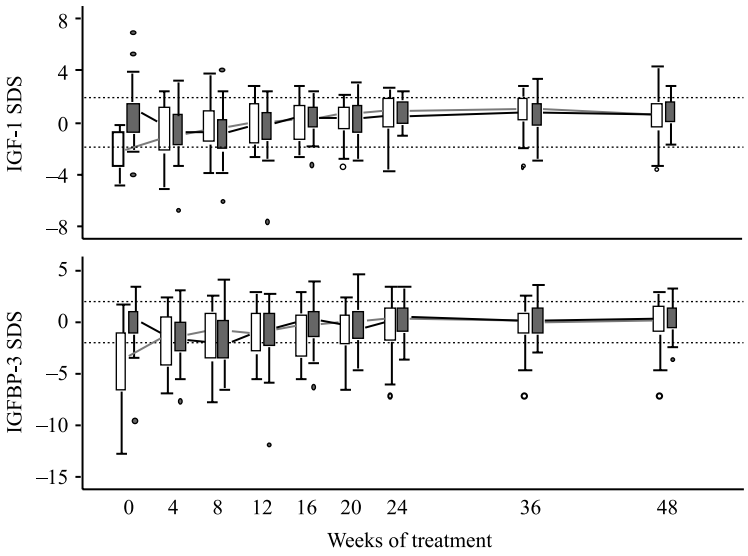

Figure 2 Time course of mean IGF-I SDS (top panel) and IGFBP-3 SDS (bottom panel) during the open-label study with 48 weeks of GH treatment of adult GHD Japanese patients; patients had previously been treated with placebo (open boxes) or GH (shaded boxes) and were then treated with individualized GH dose from week 0. Data show the 25th and 75th percentiles as the top and bottom edges of each box and the vertical lines extend from the box as far as the data extend, to a distance of at most 1.5 interquartile ranges, with values more extreme than this marked as circles; dotted horizontal lines show the normal range of 1.96 to −1.96.

Table 3 Percentage changes from baseline in LBM and fat mass during fixed-dose and individualized regimens of GH treatment in adult Japanese patients with GHD (mean±S.D. (*n*)).

			Percentage change from baseline			
Parameter	**Dose regimen (study)**	**Weeks**	PL/GH	*P* value	GH/GH	*P* value
LBM	Fixed (double-blind)	Up to week 24	−0.5±4.1 (29)	0.519*	4.7±3.9 (32)	<0.001*
	Individualized (open-label)	Up to week 24	3.4±4.8 (28)	<0.001†	0.1±4.7 (31)	–
		Up to week 48	4.5±5.3 (28)	<0.001†	1.2±4.9 (31)	–
Fat mass	Fixed (double-blind)	Up to week 24	1.1±6.9 (29)	0.388*	−9.2±11.8(32)	<0.001*
	Individualized (open-label)	Up to week 24	−8.8±9.2 (28)	<0.001†	2.4±8.8 (31)	–
		Up to week 48	−10.5±11.6 (28)	<0.001†	0.3±9.7(31)	–

* Student's *t*-test; within-group changes from baseline of double-blind study.
† Student's *t*-test; within-group changes from baseline of open-label study.

mass were statistically significantly different after 48 weeks of GH treatment in the open-label study compared with the corresponding changes in the preceding double-blind study ($P = 0.001$ for LBM and $P < 0.001$ for fat mass). Further, the changes from baseline in LBM and fat mass for the PL/GH group were significant in both AO and CO patients (Table 4) at the end of the open-label study. The changes from baseline during the individualized-dose, open-label study in the PL/GH group were similar to those achieved in the GH/GH group at the end of the 24-week, fixed-dose, double-blind study. Mean body weight and body mass index were not changed in the course of GH treatment in these studies.

The reductions in serum total cholesterol levels were significant after 24 weeks in the open-label study but not after 48 weeks in the PL/GH group (Table 5). However, the decreases observed in mean total cholesterol concentrations largely reflected those patients with abnormally high cholesterol levels at baseline. In these patients ($n = 12$) with total cholesterol over 220 mg/dl (equivalent to 5.69 mM), the change after 24 weeks of treatment was significant (baseline, 251 ± 24 mg/dl (6.49 ± 0.62 mM), 24 weeks, 219 ± 31 mg/dl (5.66 ± 0.8 mM); $P = 0.025$) but the change after 48 weeks of treatment was less evident, without statistical significance (226 ± 29 mg/dl (5.84 ± 0.75 mM); $P = 0.062$), in the PL/GH group. Decreases in serum LDL-cholesterol levels, after 48 weeks of treatment, were significant for the PL/GH group as a whole (Table 5). Again, where patients had abnormally high baseline levels (>140 mg/dl (3.62 mM)) for LDL-cholesterol, there were similar reductions at the end of the open-label study (results not shown).

Safety

The treatment-emergent adverse events observed in more than 10% of patients in either group in the double-blind and open-label studies are given in Table 6. Oedema was less frequent in both treatment groups in the individualized-dose, open study than in the GH/GH group during the fixed-dose, double-blind study treatment period. The incidence of oedema declined further in both groups between weeks 24 and 48 of the open-label study. There was an overall tendency that AO patients who received GH ($n = 25$) experienced more adverse events than CO patients who received GH ($n = 36$), such as oedema (16.0% for AO versus 5.6% for CO) and arthralgia (36.0% for AO versus 25.0% for CO). The number of serious adverse events was small (two cases in the GH/GH group and one case in the PL/GH group) in the open-label study and none occurred between weeks 24 and 48. The three serious adverse events were moderate depression (PL/GH group), severe vertigo and severe craniopharyngioma recurrence (GH/GH group). Of these events, depression and vertigo were assessed as having no causal relationship with GH. The serious adverse event of craniopharyngioma resulted in the patient being withdrawn from treat-

Table 4 Percentage changes during individualized-dose regimen of GH treatment in LBM and fat mass by onset in adult Japanese patients with GHD, in the open-label study (mean±S.D.).

			Percentage change			
			PL/GH			
Parameter	**Dose regimen (study)**	**Weeks**	AO ($n = 11$)	*P* value*	CO ($n = 17$)	*P* value
LBM	Individualized (open-label)	Up to week 24	4.7±2.7	<0.001	2.6±5.7	0.074
		Up to week 48	6.1±3.6	<0.001	3.4±5.9	0.030
Fat mass	Individualized (open-label)	Up to week 24	−11.2±11.7	0.010	−7.3±7.2	<0.001
		Up to week 48	−12.1±12.7	0.010	−9.6±11.1	0.003

*Student's *t*-test; within-group changes.

Table 5 Total and LDL-cholesterol values during the open-label, individualized-dose study of GH treatment in Japanese patients with adult GHD (mean±S.D. (*n*)).

Parameter	**Dose regimen** (study)	**Weeks**	**PL/GH** ($n = 28$)	***P* value***
Total cholesterol (mg/dl)	Individualized (open-label)	0	210±42	–
		24	193±38	0.011
		48	199±38	0.103
LDL-cholesterol (mg/dl)	Individualized (open-label)	0	127±34	–
		24	114±36	0.013
		48	116±38	0.032

*Compared with week 0; Wilcoxon signed-rank test.

Table 6 Incidence of adverse events with more than 10% frequency by MedDRA system organ class in adult Japanese GHD patients treated with placebo for 24 weeks followed by GH for 48 weeks (PL/GH) or GH throughout (GH/GH) in the fixed-dose, double-blind and individualized dose, open-label studies.

	Incidence of adverse events, *n* (% of *N*)					
	Fixed-dose study		Individualized dose study			
	24 weeks		0–24 weeks		24–48 weeks	
System organ class/adverse event	PL/GH (*n* = 31)	GH/GH (*n* = 33)	PL/GH (*n* = 28)	GH/GH (*n* = 31)	PL/GH (*n* = 28)	GH/GH (*n* = 30)
Respiratory, thoracic and mediastinal disorders	22 (71.0)	17 (51.5)	15 (53.6)	19 (61.3)	15 (53.6)	17 (56.7)
Nasopharyngitis	17 (54.8)	11 (33.3)	7 (25.0)	13 (41.9)	7 (25.0)	14 (46.7)
Cough	6 (19.4)	7 (21.2)	9 (32.1)	4 (12.9)	3 (10.7)	2 (6.7)
Rhinorrhoea	6 (19.4)	7 (21.2)	5 (17.9)	8 (25.8)	2 (7.1)	4 (13.3)
Pharyngolaryngeal pain	5 (16.1)	6 (18.2)	3 (10.7)	5 (16.1)	2 (7.1)	2 (6.7)
Upper respiratory tract inflammation	4 (12.9)	5 (15.2)	1 (3.6)	2 (6.5)	2 (7.1)	2 (6.7)
General disorders and administration site conditions	16 (51.6)	15 (45.5)	11 (39.3)	13 (41.9)	12 (42.9)	10 (33.3)
Pyrexia	12 (38.7)	7 (21.2)	4 (14.3)	5 (16.1)	7 (25.0)	7 (23.3)
Oedema	2 (6.5)	4 (12.1)	2 (7.1)	0	1 (3.6)	0
Fatigue	3 (9.7)	1 (3.0)	3 (10.7)	1 (3.2)	0	0
Musculoskeletal and connective tissue disorders	4 (12.9)	13 (39.4)	10 (35.7)	7 (22.6)	4 (14.3)	10 (33.3)
Arthralgia	4 (12.9)	6 (18.2)	5 (17.9)	2 (6.5)	1 (3.6)	6 (20.0)
Back pain	0	2 (6.1)	4 (14.3)	0	2 (7.1)	4 (13.3)
Nervous system disorders	6 (19.4)	9 (27.3)	6 (21.4)	9 (29.0)	4 (14.3)	10 (33.3)
Headache	4 (12.9)	6 (18.2)	4 (14.3)	6 (19.4)	3 (10.7)	4 (13.3)
Dizziness	0	1 (3.0)	0	2 (6.5)	1 (3.6)	4 (13.3)
Skin and subcutaneous tissue disorders	10 (32.3)	9 (27.3)	3 (10.7)	5 (16.1)	6 (21.4)	5 (16.7)
Pruritus	4 (12.9)	1 (3.0)	2 (7.1)	2 (6.5)	1 (3.6)	0
Gastrointestinal disorders	12 (38.7)	8 (24.2)	6 (21.4)	7 (22.6)	6 (21.4)	6 (20.0)
Nausea	5 (16.1)	3 (9.1)	1 (3.6)	0	0	2 (6.7)
Diarrhoea (NOS)	5 (16.1)	2 (6.1)	2 (7.1)	1 (3.2)	2 (7.1)	1 (3.3)
Metabolism and nutrition disorders	5 (16.1)	4 (12.1)	0	3 (9.7)	0	1 (3.3)
Anorexia	5 (16.1)	1 (3.0)	0	2 (6.5)	0	1 (3.3)
Investigations	3 (9.7)	5 (15.2)	2 (7.1)	1 (3.2)	3 (10.7)	7 (23.3)
Sputum increased	1 (3.2)	1 (3.0)	2 (7.1)	0	2 (7.1)	3 (10.0)

NOS, not otherwise specified.

ment; the causal relationship with GH was considered to be unknown. The prescribed dose level was reduced in the GH/GH group in five patients and in the PL/GH group in three patients due to adverse events in the open-label study. Of these adverse events, three arthralgia cases (two patients in the GH/GH group), two oedema cases (two patients in the PL/GH group), one hypertension case (GH/GH group) and one case of musculoskeletal stiffness (GH/GH group) were possibly related to GH treatment.

Mean values for all standard clinical safety laboratory parameters were within the normal reference range at the end of the open-label study. No changes from baseline in laboratory parameters or systolic and diastolic blood pressures indicated any safety problems. Following GH treatment in the PL/GH group, there was an increase from 4.5±0.6 to 4.7±0.6% in mean HbA1c, but mean values were within the normal reference range at all visits. One patient in this group had an abnormally high HbA1c level (5.9%) at the end of treatment but the value at baseline (5.6%) was already close to the upper limit of normal. There were almost no changes from baseline to the end of the open-label study in mean thyroid-stimulating hormone (0.0±0.4 mU/l), free 3,3′,5triiodothyronine (T_3; 0.3±0.9 ng/l) or free thryroxine (T_4; −0.0±0.7 ng/dl) levels in PL/GH group.

Discussion

The benefits of GH replacement for adult GHD patients are well established for Caucasian patients. Current monitoring indicates that potential safety issues have been identified and addressed in these populations (6). The genetic and environmental backgrounds of Japanese patients differ from their Caucasian counterparts although the incidence of obesity and its related complications are increasing (7, 8). A previous double-blind study indicated the benefits of GH treatment for adult Japanese GHD patients (4). In this open-label study a different approach, using an individualized dosing regimen based on IGF-I levels, was implemented to compare the effects on efficacy and safety. The open-label design of the present study may introduce more bias than a double-blind design and the results must be considered with caution. However, given the demonstrated efficacy in Caucasian patients, it was not

considered ethical to use placebo treatment for a long-term study and the open-label design is consistent with routine clinical practice.

Sensitivity to GH therapy varies considerably, particularly in the elderly (1). It has been demonstrated that use of individualized dosing regimens reduces variation in response for most endpoints, particularly between genders (9). However, this method based on serum IGF-I concentrations has not been investigated in Japanese GHD patients. In the present study such a dosing regimen allowed for more moderate dose increases compared with the fixed-dose titration method used in the initial study (4). Data from a similar study in Caucasians also showed a lower dose when using individual dose adjustment according to IGF-I compared with a fixed-dose titration (10). The final individualized dose in that study was 0.54 mg/day, which was slightly higher than the approximate daily doses in the present study, which were 0.42 mg/day for the PL/GH group and 0.48 mg/day for the GH/GH group; this is in line with what may be expected because of the higher body weight of Caucasians compared with Japanese, and would argue for dosing based on body weight in order not to overdose those of smaller, leaner body proportions.

Consistent with other studies (11), the younger CO patients were receiving a higher mean dose of GH than the older AO patients in both groups at the end of the study. Whereas this difference in dose requirements between onsets has been suggested in Caucasian patients (12), this is the first demonstration of the difference in optimal doses by onsets in Japanese GHD patients. There was a wide range of doses even within these two groups; thus, individualized treatment based on IGF-I levels indicates that optimal dosage may differ in patients with different baseline characteristics, supporting this approach to GH treatment. Despite this difference in dose, the changes in LBM and fat mass were statistically significant in both AO and CO patients in both groups. Current recommendations suggest that IGF-I and IGFBP-3 are measured as a part of the management of patients receiving GH treatment (6). High levels of IGF-I can mediate adverse drug reactions such as arthralgia. In the present study, using the dose-adjustment method, changes in IGF-I and IGFBP-3 levels were parallel and within normal limits.

The double-blind study on Japanese adult GHD patients (4) confirmed the efficacy of GH therapy over a period of 24 weeks, in agreement with results from clinical trials over 3–6 months in Caucasian subjects (13). In another trial of Japanese adult GHD patients, mean body fat was reduced after 1 month of GH therapy and this was maintained for a further 8 months (14). In the present longer-term open-label study, Japanese adult hypopituitary patients with GHD received individualized GH therapy for 48 weeks. These patients had a significant increase in LBM and decrease in fat mass. Although there was a dose reduction in the GH/GH group between the double-blind and open-label studies, they maintained the improvements in these parameters over this treatment period.

The decrease in fat mass was in accord with a significant improvement in total cholesterol and LDL-cholesterol in those patients with abnormally high levels at baseline in this individualized-dose study, and is consistent with results from other studies (15–17). These high levels were above the Japanese validation for the Framingham threshold for cardiovascular risk and hence individualized GH therapy contributed to a reduction in these risk factors (18). The higher cholesterol values observed after 48 weeks compared with 24 weeks of treatment in both groups has been observed in other clinical trials (14). GH has complex effects on lipid metabolism (19) and it may be that cholesterol levels varied during GH treatment while attaining a new equilibrium state. In Japanese children with GHD, who have been treated with GH, mean total cholesterol and total/high-density-lipoprotein-cholesterol ratio were decreased markedly in both sexes but statistical significance was detected only in boys (20). The longest-term data in Japanese paediatric male GHD patients showed that 3 years of GH replacement caused a significant decrease in LDL-cholesterol (21).

Adverse events were predominantly mild and the most frequently reported were either common events (nasopharyngitis, pyrexia) or known to be associated with GH pharmacological action (arthralgia, headache). In the early stages of GH-replacement therapy, retention of water may occur, leading to oedema, arthralgia or carpal tunnel syndrome (22). In the present study, consistent with other studies (12), GH was administered at a low dose until week 8 in the open-label study to minimize this problem. In the 48-week open-label study the incidence of oedema was lower in both the GH/GH and PL/GH groups compared with the GH/GH group in the double-blind study. This lower incidence may reflect the decreased dose consequent on the individual dosing regimen. There were only three serious adverse events during the IGF-I-controlled regimen, suggesting a safer profile of this GH modality. As might be anticipated, from the inhibitory effects of GH on insulin sensitivity, there was a slight increase in mean serum HbA1c levels in the PL/GH group. This observation is consistent with other studies on Caucasian patients (23). It has been reported that the interaction of GH with other hormones during replacement therapy accelerates the conversion of T_4 to T_3, at least in the early stages of treatment (24). However, routine monitoring of thyroid function during the present study did not indicate any changes in these parameters.

In summary, the efficacy of individualized GH-replacement therapy in adult Japanese patients has been

demonstrated. This treatment regimen conferred advantages in terms of level of dosage and safety and in treating patients with different baseline characteristics. It is recommended that the dose-adjustment method of GH administration, based on IGF-I levels, is adopted for future treatment of adult Japanese GHD patients.

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