Original Article

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Metabolic and endocrinological effects of weekly growth hormone replacement therapy with somapacitan in patients with adult growth hormone deficiency after switching from daily growth hormone replacement therapy: A real-world exploratory cohort study

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SUMMARY: The metabolic and endocrinological effects in patients with adult growth hormone deficiency (AGHD) who switched from daily growth hormone (GH) replacement therapy to weekly GH replacement therapy with somapacitan were evaluated and observed over a long follow-up period. Patients were included only if their medical treatments, aside from GH replacement therapy, remained unchanged. Metabolic and endocrinological parameters were assessed at the time of switching, and at 1- and 2-year follow-up after switching from daily GH replacement therapy to weekly GH replacement therapy with somapacitan. The results showed that the body mass index (BMI), fasting plasma glucose (FPG), aspartate transaminase (AST), and triglyceride (TG) levels at 1 year after switching significantly improved compared with those at the time of switching (each $P < 0.025$). At 2 years, the homeostasis model assessment of insulin resistance (HOMA-IR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and alanine aminotransferase (ALT), as well as BMI, FPG, TG, and AST significantly improved compared with those observed at the time of switching (each $P < 0.025$). In addition, improvement in HOMA-IR at 2 years after switching was significantly associated with improvement in AST. Switching to GH replacement therapy did not affect endocrinological parameters. These findings, which were revealed by the present real-world exploratory cohort study, indicate that weekly GH replacement therapy with somapacitan may confer more beneficial effects than daily GH replacement therapy.

Keywords: Growth hormone, adult growth hormone deficiency, somapacitan

1. Introduction

Adult growth hormone deficiency (AGHD) is an anterior pituitary hormonal deficiency (*1,2*). AGHD causes fatty liver, metabolic dysfunction-associated steatohepatitis (MASH), metabolic dysfunction-associated steatotic liver disease (MASLD), increased visceral adiposity, osteoporosis, impaired quality of life (QOL), poor concentration, inattention, coronary artery disease, and heart failure (*3-10*). Accordingly, AGHD may be associated with increased mortality. Growth hormone (GH) replacement therapy has been reported to reduce mortality in patients with AGHD (*10*). Therefore, GH replacement therapy is essential for patients with AGHD. Globally, daily GH replacement therapy had long been the only available treatment for patients with AGHD. It is well known that GH concentrations in the blood are normally high at midnight and are low during the day, whereas GH concentrations in patients with AGHD are extremely low throughout the day. Thus, patients with AGHD commonly self-inject GH formulations nightly (between 7:00 pm and 8.00 pm). However, blood GH concentrations of patients with AGHD during the daytime remain severely low compared with those in normal subjects, as the duration of daily GH formulations is less than 12 h (*11,12*). Recently, patients with AGHD

have been able to use somapacitan, the only available weekly GH formulation. Nevertheless, the prolonged duration of somapacitan exceeds 1 week, and the effects of this formulation are maintained throughout the day. Considering the differences in duration, metabolic and endocrinological parameters may differ between daily GH replacement therapy and weekly GH replacement therapy with somapacitan. Previously, we reported a real-world pilot study that revealed that the body mass index (BMI), homeostasis model assessment of insulin resistance (HOMA-IR), fasting plasma glucose (FPG), and liver function parameters were significantly improved 6 months after switching from daily GH replacement therapy to weekly GH replacement therapy with somapacitan compared with those observed at the time of switching (*13*). In the present study, we measured and compared the metabolic and endocrinological parameters at the time of switching from daily GH replacement to weekly GH replacement therapy with somapacitan, and at 1- and 2-year follow-up after switching in patients with AGHD.

2. Patients and Methods

2.1. Ethical approval of the study protocol

This real-world exploratory cohort study protocol was approved by the ethics review committees of Fukuoka University (Fukuoka, Japan. Approval number: C25-09-006). Written informed consent was obtained from all participants in the study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Study participants

We investigated 12 individuals with AGHD who had been diagnosed on the basis of no or inadequate GH responses to a GH-releasing peptide-2 test, insulin tolerance test, or arginine test at Fukuoka University Chikushi Hospital and Nagasaki Prefecture Iki Hospital (*13-15*). All patients had received daily GH replacement therapy for over 2 years and switched to weekly GH replacement therapy with somapacitan, which was continued for 2 years. No medical treatments other than GH replacement therapy were changed during the evaluation period.

2.3. Methods and disease definitions

We administered somapacitan for 2 years in patients with AGHD who had previously received daily GH replacement therapy. The starting dose at the time of switching were 1.5 mg/week for adults aged 18-60 years and 1.0 mg/week for patients aged > 60 years, in accordance with recommendation from a phase 3 trial in Japan (REAL Japan) (*16*). Dose titration was performed according to the insulin-like growth factor 1 (IGF1) levels, as described in our previous study (*13*). The following variables were examined at the time of switching, and at 1- and 2-year follow-up after switching: parameters of glucose control (glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and homeostasis model assessment of β-cell function (HOMA-β), markers of lipid metabolism (low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG), liver function parameters (aspartate transaminase (AST), alanine transaminase (ALT), and gamma-glutamyl transferase (γ-GTP)), estimated glomerular filtration rate (eGFR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and BMI. Blood samples were obtained after overnight fasting.

Regarding assessment of insulin secretion, HOMA-β was calculated using the following formula:

$$\text{HOMA-}\beta = 360 \times \text{fasting insulin } (\mu\text{U/mL})/(\text{FPG (mg/dL)} - 63)$$

Regarding assessment of insulin resistance, HOMA-IR was calculated using the following formula:

$$\text{HOMA-IR} = \text{FPG (mg/dL)} \times \text{fasting insulin } (\mu\text{U/mL})/405$$

Endocrinologically, anterior pituitary hormones and related hormones (adrenocorticotropic hormone (ACTH), cortisol, thyroid-stimulating hormone (TSH), free thyroxine 4 (T4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone [male]/estradiol [female]) were measured at the time of switching, and at 1 and 2 years after switching. ACTH deficiency was diagnosed by a combination of reduced ACTH and cortisol levels in the morning and no or inadequate changes in ACTH or cortisol levels after a corticotropin-releasing hormone test. TSH deficiency was diagnosed on the basis of a combination of reduced TSH levels, no or inadequate changes in TSH levels after a thyrotropin-releasing hormone test, and existing secondary hypothyroidism. LH or FSH deficiency was diagnosed on the basis of a combination of reduced LH or FSH levels, no or inadequate changes in LH or FSH levels after an LH-releasing hormone test, and existing secondary hypogonadism. Central diabetes insipidus was diagnosed by a combination of increased urinary volume, low urinary osmolarity, low antidiuretic hormone (ADH) levels compared with serum osmolarity, no or inadequate changes in ADH levels after a water restriction test or 5% NaCl loading test, and increased ADH levels with decreased urinary volume after 1-desamino-8-D-arginine vasopressin administration (*13-15*).

No medical treatments other than GH replacement therapy were changed during the study period.

2.4. Statistical analyses

Data are presented as mean ± standard deviation (SD). Statistical analyses were performed using Stata SE v.16 (StataCorp 2019, Stata statistical software Release 16. [College Station, TX: Stata Corp LLC]). A paired *t*-test with Dunnett's correction was used to compare the means of laboratory measurements between the time of switching and 1 year after switching, as well as between the time of switching and 2 years after switching. *P*-values < 0.025 were considered significant. Associations between improvements in HOMA-IR and other parameters were examined using univariate regression analysis, and *P*-values < 0.05 were considered statistically significant.

3. Results

Table 1 presents the baseline characteristics of the patients enrolled in the present study. All patients had AGHD and were receiving daily GH replacement therapy. The mean age was 60.3 ± 18.9 years, and nine patients were female. The BMI was 26.4 ± 5.1. Endocrinologically, 75.0%, 58.3%, 50.0%, and 50.0% of the patients exhibited ACTH, TSH, LH, and FSH deficiencies, respectively. A total of 8.3% of patients had central diabetes insipidus. In addition, hydrocortisone, levothyroxine, human chorionic gonadotrophin/human menopausal gonadotropin (HCG/HMG), and testosterone/estrogen, and desmopressin replacement therapy were administered in 75.0, 66.7, 8.3, 0.0, and 8.3% of patients, respectively (one patient had primary hypothyroidism rather than TSH deficiency and was administered levothyroxine). As a result of titration, IGF1 values at 1 and 2 years after switching to somapacitan were comparable to those at the time of switching (103.5 ± 43.8 at switching *vs.* 95.2 ± 43.2 ng/mL at 1 year, *P* = 0.121; and 101.2 ± 35.2 ng/mL at 2 years, *P* = 0.352). Moreover, the IGF1 values of all patients at the time of switching to somapacitan and at 1 and 2 years after switching were between -1 SDS and +1 SDS. The mean dose of daily GH replacement at the time of switching was 0.20 ± 0.07 mg/day, and the dose of somapacitan at 1 and 2 years after switching was 1.60 ± 0.49/1.88 ± 0.61 mg/week, respectively (Table 2).

Table 3 shows the changes achieved in clinical, metabolic, and endocrinological parameters. In terms of glucose tolerance, FPG was significantly improved at 1 year after switching compared with values at the time of switching (102.8 ± 19.5 *vs.* 97.3 ± 20.3 mg/dL, *P* = 0.024). HbA1c, fasting insulin, HOMA-IR, and HOMA-β did not improve from the time of switching to 1 year after switching (HbA1c: 6.2 ± 0.5 *vs.* 6.2 ± 0.6 %, *P* = 0.403, fasting insulin: 11.6 ± 7.5 *vs.* 8.3 ± 7.2 μU/mL, *P* = 0.028, HOMA-IR: 2.8 ± 1.6 *vs.* 2.0 ± 1.7 , *P* = 0.029, HOMA-β: 137.8 ± 132.3 *vs.* 105.4 ± 92.3, *P* = 0.080). Meanwhile, HOMA-IR and FPG significantly improved from the time of switching to 2 years after switching (HOMA-IR: 2.8 ± 1.6 *vs.* 2.1 ± 1.1, *P* = 0.024, FPG: 102.8 ± 19.5 *vs.* 97.5 ± 18.9 mg/dL, *P* = 0.010). HbA1c, fasting insulin, and HOMA-β did not improve from the time of switching to 2 years after switching (HbA1c: 6.2 ± 0.5 *vs.* 6.2 ± 0.6 %, *P* = 0.330, fasting

Table 1. Summary of patient characteristics

	Number of patients = 12
Age (years, ± SD)	60.3 ± 18.9
Sex (Female/Male)	9/3
BMI (kg/m^2, ± SD)	26.4 ± 5.1
Hormonal deficiencies	
ACTH (%)	75.0
TSH (%)	58.3
LH (%)	50.0
FSH (%)	50.0
Central diabetes insipidus (%)	8.3
GH (%)	100
Replacement therapies	
Hydrocortisone (%)	75.0
Levothyroxine (%)	66.7[#]
HCG/HMG (%)	8.3
Testosterone/Estrogen(%)	0
Desmopressin (%)	8.3
GH (%)	100
Periods of GH replacement therapy (years, ± SD)	7.2 ± 2.9

[#]One patient received levothyroxine for primary hypothyroidism. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; TSH, thyroid-stimulating hormone; HCG, human chorionic gonadotropin; HMG, human menopausal gonadotropin; LH, luteinizing hormone; SD, standard deviation.

Table 2. Details of GH replacement therapy in our study

	At switching (0)	1 year after switching (1)	*P*-value (0 *vs.* 1)	2 years after switching (2)	*P*-value (0 *vs.* 2)
IGF-1 (ng/mL, ± SD)	103.5 ± 43.8	95.2 ± 43.2	0.121	101.2 ± 35.2	0.352
Daily dose of GH before switching (mg/day, ± SD)	0.20 ± 0.07	-	-	-	-
Weekly dose of GH 1 year after switching (mg/week, ± SD)	-	1.60 ± 0.49	-	-	-
Weekly dose of GH 2 years after switching (mg/week, ± SD)	-	-	-	1.88 ± 0.61	-

Significant differences between mean values were estimated using a paired *t*-test with Dunnett's correction. *P* < 0.025 was considered significant. GH, growth hormone; IGF1, insulin-like growth factor-1; SD, standard deviation.

insulin: 11.6 ± 7.5 *vs.* 8.6 ± 4.7 μU/mL, $P = 0.045$, HOMA-β: 137.8 ± 132.3 *vs.* 108.8 ± 74.3, $P = 0.112$).

TG, a marker of lipid metabolism, significantly improved from the time of switching compared with 1 and 2 years after switching (136.5 ± 39.2 at switching *vs.* 101.3 ± 74.3 at 1 year, $P = 0.006$; and 95.6 ± 29.3 at 2 years, $P < 0.001$).

Regarding liver function, AST levels significantly improved from the time of switching to 1 and 2 years after switching (23.1 ± 3.4 at switching *vs.* 21.3 ± 4.0 at 1 year, $P = 0.019$; and 20.3 ± 3.1 at 2 years, $P = 0.006$). Meanwhile, ALT improved from the time of switching to 1 year after switching but with no significant difference (19.3 ± 5.5 *vs.* 16.7 ± 5.1, $P = 0.044$), although it improved significantly from the time of switching to 2 years after switching (19.3 ± 5.5 *vs.* 15.7 ± 6.1, $P = 0.024$).

In addition, with regard to clinical parameters, BMI significantly improved from the time of switching to 1 and 2 years after switching (26.4 ± 5.1 at switching *vs.* 25.8 ± 5.3 kg/m^2 at 1 year, $P = 0.015$; and 25.7 ± 5.3 kg/m^2 at 2 years, $P = 0.009$). In addition, SBP and DBP improved from the time of switching to 1 and 2 years after switching. Furthermore, significant changes were observed from the time of switching to 2 years after switching (SBP: 139.4 ± 17.2 *vs.* 130.2 ± 16.4 mmHg, $P = 0.023$; DBP: 80.5 ± 11.1 *vs.* 73.6 ± 9.6 mmHg, $P = 0.022$).

Regarding endocrinological parameters, no differences were observed between values at the time of switching and those at 1 and 2 years after switching for all anterior pituitary hormones and related hormones.

Besides, regression analysis showed that improvement in AST levels was significantly associated with improvement in HOMA-IR ($P = 0.026$), whereas improvement in BMI, SBP, DBP, ALT, γ-GTP, and the period of daily GH replacement therapy were not significantly associated with improvement in HOMA-IR (Table 4).

4. Discussion

AGHD is a pituitary hormonal deficiency, including anterior pituitary hormonal deficiency and diabetes insipidus. Patients with severe AGHD exhibit different types of metabolic disorders (*3-10*). AGHD is associated

Table 3. Comparison of changes in metabolic and endocrinological parameters at switching from daily to weekly GH replacement therapy with somapacitan and at 1 and 2 years after switching

	at switching (0)	1 year after switching (1)	*P* (0 *vs* 1)	2 years after switching (2)	*P* (0 *vs* 2)
BMI (kg/m^2, ± SD)	26.4 ± 5.1	25.8 ± 5.3	0.015*	25.7 ± 5.3	0.009*
SBP (mmHg, ± SD)	139.4 ± 17.2	132.7 ± 15.9	0.036	130.2 ± 16.4	0.023*
DBP (mmHg, ± SD)	80.5 ± 11.1	75.9 ± 9.9	0.053	73.6 ± 9.6	0.022*
FPG (mg/dL, ± SD)	102.8 ± 19.5	97.3 ± 20.3	0.024*	97.5 ± 18.9	0.010*
HbA1c (%, ± SD)	6.2 ± 0.5	6.2 ± 0.6	0.403	6.2 ± 0.6	0.330
Fasting insulin (μIU/mL, ± SD)	11.6 ± 7.5	8.3 ± 7.2	0.028	8.6 ± 4.7	0.045
HOMA-IR (± SD)	2.8 ± 1.6	2.0 ± 1.7	0.029	2.1 ± 1.1	0.024*
HOMA-β (± SD)	137.8 ± 132.3	105.4 ± 92.3	0.080	108.8 ± 74.3	0.112
AST (U/L, ± SD)	23.1 ± 3.4	21.3 ± 4.0	0.019*	20.3 ± 3.1	0.006*
ALT (U/L, ± SD)	19.3 ± 5.5	16.7 ± 5.1	0.044	15.7 ± 6.1	0.024*
γ-GTP (U/L, ± SD)	24.0 ± 16.1	21.5 ± 14.0	0.033	21.7 ± 11.7	0.143
LDL-C (mg/dL, ± SD)	111.2 ± 23.5	104.8 ± 21.6	0.167	104.3 ± 22.2	0.142
HDL-C (mg/dL, ± SD)	59.8 ± 8.5	55.8 ± 8.7	0.042	60.3 ± 10.6	0.427
TG (mg/dL, ± SD)	136.5 ± 39.2	101.3 ± 24.7	0.006*	95.6 ± 29.3	< 0.001*
eGFR (mL/min/1.73m^2)	66.8 ± 23.9	66.2 ± 22.7	0.355	66.6 ± 23.1	0.452
Na (mmol/L, ± SD)	141.5 ± 2.7	141.9 ± 2.0	0.313	141.8 ± 3.1	0.376
K (mmol/L, ± SD)	3.9 ± 0.3	4.0 ± 0.7	0.255	3.8 ± 0.4	0.276
Cl (mmol/L, ± SD)	105.0 ± 2.1	104.8 ± 2.1	0.219	105.3 ± 1.9	0.369
ACTH (pg/mL, ± SD)	18.0 ± 21.6	20.1 ± 24.5	0.155	19.0 ± 23.8	0.215
Cortisol (μg/dL, ± SD)	5.3 ± 4.0	5.9 ± 4.4	0.229	5.3 ± 4.5	0.481
TSH (μIU/mL, ± SD)	1.9 ± 1.4	1.9 ± 1.4	0.416	1.8 ± 1.1	0.370
Free T4 (ng/dL, ± SD)	0.9 ± 0.1	1.0 ± 0.2	0.064	1.0 ± 0.2	0.053
PRL (ng/mL, ± SD)	14.6 ± 13.3	12.3 ± 10.5	0.060	11.4 ± 9.5	0.068
LH (mIU/mL, ± SD)	2.5 ± 1.6	3.7 ± 2.9	0.058	3.2 ± 2.6	0.102
FSH (mIU/mL, ± SD)	4.8 ± 3.7	4.7 ± 3.6	0.305	5.2 ± 3.9	0.028
Testosterone (ng/mL, ± SD) (Male only)	4.7 ± 3.0	6.1 ± 4.8	0.175	2.1 ± 1.7	0.203
Estradiol (pg/mL, ± SD) (Female only)	25.5 ± 61.0	60.2 ± 136.0	0.207	33.6 ±77.2	0.092

Significant differences between mean values were estimated using a paired *t*-test with Dunnett's correction. *$P < 0.025$ was considered significant. ACTH, adrenocorticotropic hormone; AST, aspartate transaminase; ALT, alanine aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FSH, follicle-stimulating hormone; FPG; fasting plasma glucose; γ-GTP, γ-glutamyl transferase; HbA1c, glycated hemoglobin; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LH, luteinizing hormone; PRL, prolactin; SBP, systolic blood pressure; SD, standard deviation; T4, thyroxine 4; TG, triglycerides; TSH, thyroid-stimulating hormone.

Table 4. Relationship between improvement in HOMA-IR and other parameters

Regression analysis	Improvement in HOMA-IR		
	β (SE)	95% CI	*P*-value
Improvement in BMI	2.260 (2.560)	-3.525-8.045	0.405
Improvement in SBP	0.487 (0.764)	-1.215-2.189	0.538
Improvement in DBP	0.452 (0.629)	-0.949-1.853	0.489
Improvement in AST	1.195 (0.456)	0.178-2.212	0.026*
Improvement in ALT	0.465 (0.327)	-0.263-1.194	0.185
Improvement in γ-GTP	0.554 (0.432)	-0.408-1.516	0.228
Periods of daily GH replacement therapy	-3.461 (2.755)	-9.198-2.276	0.209

Significant associations between mean values were estimated using a univariate regression analysis. *$P < 0.05$ was considered significant. AST, aspartate transaminase; ALT, alanine aminotransferase; β, regression coefficient; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; GH, growth hormone; HOMA-IR, homeostasis model assessment of insulin resistance; CI, confidence interval; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; SBP, systolic blood pressure; SE, standard error.

with obesity, dyslipidemia, MASH/MASLD, increased insulin resistance, and increased risk of coronary heart disease (*17-19*). Considering the improvements in BMI, weekly GH replacement therapy with somapacitan may be more beneficial than daily GH replacement therapy. Regarding liver dysfunction, AST and ALT levels were significantly improved by switching from daily GH replacement therapy to weekly GH replacement therapy with somapacitan, and levels at 2 years after switching showed more effective results than those at 1 year after switching. AGHD is well-known to cause MASH/MASLD (*3,18,19*). Similarly, TG levels significantly improved after switching from daily GH replacement therapy to weekly GH replacement therapy with somapacitan. and levels at 2 years after switching were lower than those at 1 year after switching. Besides, SBP and DBP at 2 years after switching were significantly improved compared with values at the time switching, whereas SBP and DBP at 1 year after switching were improved compared with those at the time of switching treatment, but were not significantly improved. These results are consistent with those of a previous report, which revealed that GH replacement therapy could decrease SBP and DBP in patients with AGHD (*6*). Considering that improvements in the lipid profile and blood pressure reduce the risk of coronary heart disease, weekly GH replacement therapy with somapacitan may be more beneficial than daily GH replacement therapy. Furthermore, FPG levels significantly improved after switching from daily GH replacement therapy to weekly GH replacement therapy with somapacitan, and levels at 2 years after switching showed more effective results than those at 1 year after switching. In addition, HOMA-IR values at 2 years after switching were significantly improved compared with those at the time switching. Although HOMA-IR values at 1 year after switching were improved compared with those at the time of switching treatment, but were not significantly improved.

Considering these data and the lack of change in HOMA-β levels, the improvement in FPG might be due to the improvement in insulin resistance. Previously, we reported that HOMA-IR significantly improved from the time of switching treatment to the 6-month follow-up. However, no significant differences in glucose intolerance were observed between daily GH replacement therapy and weekly GH replacement therapy with somapacitan, which contrasted with the data from a phase 3 clinical trial (*20*). The differences between the trial findings and our results could be because the medical treatment of all patients in the present study did not change during this period, aside from GH formulations, although it is quite possible that medical treatment may have changed in some patients in the phase 3 trials of somapacitan (*16,21,22*). However, a post hoc analysis of one of the phase 3 studies indicated that the group receiving somapacitan had significantly lower HOMA-IR and FPG levels than those receiving daily GH formulations 32 weeks after treatment initiation, which was similar to the results of our present and previous studies. Nevertheless, several factors regulate insulin resistance. Regression analysis revealed that an improvement in AST levels was significantly associated with an improvement in HOMA-IR ($P = 0.026$). In contrast, an improvement in BMI was not significantly associated with an improvement in HOMA-IR. In addition, a previous clinical trial showed no significant differences in the body composition of patients following daily GH formulations and somapacitan treatment (*22*). Patients with AGHD may exhibit excessive hepatic insulin resistance caused by fatty liver, MASH, or MASLD (*23*). Hence, the present study revealed that weekly GH replacement therapy with somapacitan may confer more beneficial effects on improving insulin resistance by ameliorating hepatic insulin resistance than daily GH replacement therapy. In our previous study, albeit over a short follow-up period, the results indicated that improvement in HOMA-IR was significantly associated with the duration of daily GH replacement therapy before switching to weekly GH

replacement therapy with somapacitan. These findings suggest that daily GH replacement formulations could be less efficient, at least for glucose intolerance, than weekly GH replacement therapy with somapacitan. Switching to weekly GH replacement therapy with somapacitan should be considered as soon as possible if patients with AGHD are currently being treated with daily GH replacement therapy. However, in the present study, no significant association was observed between an improvement in HOMA-IR and the period of daily GH replacement therapy before switching to weekly GH replacement therapy with somapacitan. This discrepancy indicated that a longer period of weekly GH replacement therapy with somapacitan could reduce increased insulin resistance in patients who receive prolonged daily GH replacement therapy.

In the present study, we demonstrated that switching to GH replacement therapy did not affect endocrinological parameters, similar to our previous real-world pilot study (*13*). Hence, somapacitan can be used without impairing the endocrinological condition of patients.

Meanwhile, the present study has some limitations that should be acknowledged. First, the sample size was small because AGHD is a rare and intractable condition. Furthermore, we excluded patients whose medical treatments, aside from GH replacement therapy, changed during the study period. This could be the reason that the levels of HbA1c at 1 year and 2 years after switching were not significantly improved compared to those at switching. However, considering the levels of HOMA-IR were significantly improved at 2 years after switching, the levels of HbA1c could be improved with longer examination. Therefore, future studies with a larger cohort comparing groups receiving weekly GH replacement therapy with somapacitan and those receiving daily GH replacement therapy for a longer period are required. Similarly, to confirm the observed univariate association between improvements in AST and HOMA-IR, future studies with large cohort are also required. Second, we used HOMA-IR and HOMA-β as surrogate markers of insulin resistance, and insulin secretion as a substitute for an oral glucose tolerance test or hyperglycemic/hyperinsulinemic–euglycemic clamps.

Therefore, future studies with a larger cohort comparing groups receiving weekly GH replacement therapy with somapacitan and those receiving daily GH replacement therapy are required to confirm the results of the present study.

In conclusion, this study revealed that weekly GH replacement therapy with somapacitan may achieve more beneficial effects on metabolic parameters than daily GH replacement therapy alone. Furthermore, the present study indicated that weekly GH replacement therapy with somapacitan could improve glucose intolerance by reducing hepatic insulin resistance compared with daily GH replacement therapy.

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