Changes, limitations, and prospects of adult height in GH treatment for Japanese GHD patients

Toshiaki Tanaka
Tanaka Growth Clinic, Tokyo, Japan

Abstract: For the treatment of pituitary dwarfism (called pituitary short stature in 1987 and renamed as growth hormone deficiency [GHD] in 1993), pituitary-derived human growth hormone (phGH) was approved in 1975, and recombinant hGH (rhGH) was approved in 1988. Adult height in patients with isolated GH deficiency (IGHD) improved by 2000. However, this improvement was mainly due to the increase in height SDS at GH treatment initiation. Although the mean adult height in patients with idiopathic GHD has been reported to be approximately –1.0 SD or higher in Europe and the United States, the mean adult height of patients with idiopathic GHD in Japan has not improved as much as that in Europe and the United States after 2000. The possible reasons were: low therapeutic doses than those in Europe and the United States; changes in background factors, such as reduction in severe GHD; differences in response to GH between Caucasians and Japanese; and, no increase in height at puberty onset because delayed pubertal onset of GHD by early GH treatment.

Key words: GH deficiency (GHD), adult height, pituitary-derived human GH (phGH), recombinant hGH (rhGH), long-acting GH

Highlights

- Adult height in GH-treated GHD had been improved from the phGH period to the early rhGH period mainly because of the improvement in height SDS at GH treatment initiation.
- Until the early rhGH period, the diagnostic criteria, subsidy system of the Ministry of Health and Welfare (later the Ministry of Health, Labor and Welfare), and background characteristics of GHD had been changed.
- Since 2000, adult height of Japanese patients with GHD has not improved because of a single low GH dose, low response to GH compared with that in Caucasians, and the normalization of delayed pubertal onset of GHD by early GH treatment.
Initiation of GH Treatment for GHD Patients in Japan (1)

The first human growth hormone (hGH) formally approved for the treatment of pituitary dwarfism in Japan was Corpormorn®, a pituitary-derived human growth hormone (phGH) imported from Kabi, Sweden, in 1975. As there was no pharmaceutical company that manufactured phGH in Japan, four types of phGH were imported and sold thereafter for the treatment of pituitary dwarfism. As all clinical trials used a therapeutic dose of 0.5 IU/kg/wk, the therapeutic dose was 0.5 IU/kg/wk, that was divided into two to three intramuscular injections. Self-injection was not approved at that time; therefore, patients had to visit the hospital for injection. Self-injection was first approved in 1981.

“The Diagnostic Guidance for Pituitary Dwarfism” prepared in 1974 by the Study Group on Pituitary Insufficiency (later the Study Group on Pituitary Dysfunction) of the Ministry of Health and Welfare (MHW) included patients with pituitary dwarfism as defined by the criteria, “primary symptom: height SDS ≤ –3.0 SD, laboratory findings: all peak GH levels ≤ 5 ng/mL in two or more GH stimulation tests”. The import volume of phGH was small; thus, to distribute it fairly, specialists nationwide organized the “Study Group of Pituitary Dwarfism Treatment” in 1974, where the indications were determined. When the Foundation for Growth Science (FGS) was established in 1977, indication judgement was transferred to the FGS.

Although the importation of phGH increased, there were more patients, with 200 to 300 waiting patients each year, until recombinant methionyl hGH (mhGH) was approved in 1986. During this period, half the dose of phGH for one patient was administered to two patients, and concomitant anabolic hormones were frequently administered to compensate for the shortage.

With the Grand-in-Aid Program for Chronic Diseases in Childhood by the Maternal and Child Health Division of MHW, patient copayment for health insurance treatment has been fully subsidized since 1975 (1).

Changes from the phGH Era to the rhGH Era

1) Changes in the diagnostic criteria

The Study Group on Hypothalamic and Pituitary Disorder changed the diagnostic term to “pituitary short stature” in 1984 and “growth hormone deficiency (GHD)” in 1993. The diagnostic criteria were changed to “primary symptom: height SDS ≤ -2.5 SD; laboratory findings: peak GH level ≤ 7 ng/mL” in 1984, to “primary symptom: height SDS ≤ -2.0 SD” in 1987, and to “laboratory findings: peak GH level ≤ 10 ng/mL” in 1993, with imports of unlimited rhGH and the harmonization of international diagnostic criteria. However, the reference peak GH level for the diagnosis of GHD had poor clinical evidence. Simultaneously, it was set as “below the reference peak GH in two or more GH stimulation tests” since 1984. Therefore, even if a GH level above the reference peak level is observed in the stimulation test, patients can be treated as having GHD if the level was below the reference peak GH in the two GH stimulation tests. Although this situation is defined as mild GHD in Japan, globally, mild GHD is not accepted as GHD but as idiopathic short stature (ISS). The severity classification was introduced in the updated “Diagnostic Guidelines” by the Study Group on the Hypothalamic and Pituitary Disorder in 1993. In all the GH stimulation tests, a maximum peak GH level of 5 ng/mL or less was considered as the complete type, and others were considered as incomplete types; this was rephrased as severe/moderate in 1999 (1). With the standardization of measured values of GH in 2004 (2), a maximum peak GH level of 3 ng/mL or less was classified as severe. In 2007, a maximum peak GH level of 3–6 ng/mL was classified as moderate, and patients other than those with severe and moderate GHD were classified as having mild GHD. In 1975, the target population for the treatment of GHD was only those with severe GHD, according to the current classification, but it has been expanded to moderate and mild cases since 1984.

2) Changes in GH measurement

The diagnosis of GHD is based on the peak GH level in the GH stimulation test. Blood GH levels were initially measured using radioimmunoassay (RIA). However, the sensitivity of RIA measurement was poor, and the initial reference peak GH level of 5 ng/mL was close to the measurement sensitivity level of RIA. Later on, several measurement methods were developed, including immunoradiometric assay (IRMA), immunoenzymometric assay (IEMA), and chemiluminescent enzyme immunoassay (CLEIA). Each measurement kit used its own phGH standard. As the immunological potency of phGH was different among the purification batches, the differences in the measured values were approximately doubled, depending on the kit. Until the measured value was adjusted using a correction formula for each kit by the GH and its Related Factors Study Committee of the FGS in 1991 (3), prior diagnoses varied depending on the assay kits. The difference in the immunological potency of phGH standards existed until 2004, when the rhGH standard was introduced into GH measurement kits. Simultaneously, differences in the measured values among the kits were minimized because of the homogeneity of the rhGH standard, and the correction formula for each kit was abolished. However, because of the difference between the immunological potencies of phGH and rhGH, the reference peak GH level was changed from 10 ng/mL to 6 ng/mL. While preparing the correction formula for each kit, the standard GH value was adjusted to the mean of the measured values. Therefore, the reference peak GH level also depended on
the mean of the measured values, and the real reference peak GH level for the diagnosis could not be followed.

3) Change in severity of GHD

According to Hibi et al. (4), in the early phGH period, breech delivery and birth asphyxia were considered to be the causes of GHD, and many of these patients had severe GHD. The Registration System Committee of the FGS examined 28,842 enrolled GHD patients (19,410 boys, 9,432 girls) from 1986 to 1995 (5). The patients were divided into three groups according to the maximum peak GH level in the GH stimulation test: ≤ 5 ng/mL (severe), > 5 to ≤ 10 ng/mL (moderate), and > 10 ng/mL (mild). Fig. 1 shows the percentage of the severity classification of idiopathic GHD for each year. The percentage of patients with severe GHD gradually decreased from 32.2% in 1986 to 8.2% in 1995. The percentage of patients with moderate GHD slightly decreased from 55.6% to 40.6%, whereas the percentage of patients with mild GHD markedly increased from 12.2% to 51.2%.

In 1997, the subsidy for the Grand-in-Aid Program for Chronic Diseases in Childhood was applicable only to moderate/severe cases with height SDS of −2.5 SD or lower, and the criteria for IGF-I were also more strictly established. Simultaneously, the number of applications registered to the FGS dropped sharply because of the FGS’s treatment indication decision, which was previously required to determine the subsidy for the Grand-in-Aid Program for Chronic Diseases in Childhood and was no longer necessary. The number of patients who received GH treatment also decreased. The number of GHD cases registered in the FGS decreased from the range of 4000 in 1997 to that of 2000 in 1998 to that of 1000 in 1999. The percentage of patients with mild idiopathic GHD who registered in the FGS from 1996 to 1997, 1998 to 2004, and 2005 to 2015 decreased to 39.5%, 31.2%, and 13.6%, respectively (6). However, as the local government’s medical subsidy program for children has been enhanced since 2001, the treatment of mild GHD has increased, but the actual number of GHD patients after 1997 cannot be determined.

Since 2000, the percentage of patients with multiple pituitary hormone deficiency (MPHD) and severe GHD has decreased. The percentage of patients with MPHD was 19.4% in the report by Hibi et al. in 1989 (4), but it decreased to 13.3% with phGH treatment and 6.2% with rhGH treatment in the report by Tanaka et al. in 2001 (7); 5.6% in the report by Ogawa et al. in 2012 (8); and, 2.8% in the report by Tanaka et al. in 2018 (9). The incidence of severe GHD was 22.8% in the report by Fujieda et al. (10) in 2010, but it decreased to 12.4% in the report by Ogawa et al. (8) in 2012 and 9.3% in the report by Tanaka et al. (9) in 2018.

Fig. 2 shows the changes in the mode of delivery in patients with idiopathic GHD during this period (5). There was no marked change in the percentage of cephalic deliveries, but the percentage of breech deliveries decreased from 11.5% in 1986 to 6.0% in 1995. The percentage of delivery by cesarean section increased from 0.8% to 8.9%. Therefore, the decrease in patients with severe GHD may be related to the decrease in breech delivery; however, because the percentage

![Fig. 1. Comparison of height SD scores at the start of GH treatment in isolated GHD during the phGH and early rhGH periods.](image-url)
of breech delivery was almost consistent after 1990, the subsequent decrease in patients with severe GHD cannot be explained. When the percentage of patients with severe GHD was examined annually by comparing breech and cephalic deliveries, the percentage of GHD patients whose disease became severe among those who were born by breech delivery and cephalic delivery in 1985 was 60.4% and 28.4%, respectively, (Fig. 3); however, these percentages decreased to 9.6% and 8.0%, respectively, in 1995 (5). The incidence of severe GHD decreased in both breech and cephalic deliveries, suggesting that the management of delivery in obstetrics has improved.

**Adult Height in hGH-Treated GHD**

1) **Adult height in the phGH period**

During the phGH period, patients with GHD were unable to receive hGH without an attending physician submitting their treatment application and reporting to the FGS. Therefore, all patients’ treatment results
were recorded in the FGS, making it the largest database on hGH treatment in Japan. Based on an analysis of this database, many articles have been published that contributed to the development of GH treatment in Japan. Reports of adult height after the first GH treatment in Japan were also the results of the FGS database analysis (4).

Hibi and Tanaka (4) reported the adult heights of 108 patients with isolated growth hormone deficiency (IGHD) registered in the FGS, who had been treated with phGH between 1975 and 1986, and those of 26 patients with MPHD complicated by gonadal dysfunction who had been treated at the National Children’s Hospital. The mean adult heights were 151.8 and 141.4 cm in males and females with IGHD and 163.7 and 151.0 cm in males and females with MPHD, respectively. Group P1 in Fig. 4 (a) and (b) indicates IGHD and MPHD in this report as the early phGH period. In addition, height SDS at the start of GH treatment were positively correlated with adult height (IGHD: r = 0.43, p<0.001; MPHD: r=0.39, p<0.05), height at the onset of puberty were positively correlated with adult height (IGHD boys: r=0.60, p<0.01,

![Graph showing adult height comparison](image_url)

**Fig. 4.** (a) Comparison of adult height after GH treatment in boys during the phGH and early rhGH periods. Group P1: Patients treated with phGH from 1975 to 1986 (Hibi, 1989). Group P2: Patients treated with phGH from 1986 to 1989 (Tanaka, 2001). Group R: Patients treated with rhGH from 1989 to 2000. (b) Comparison of adult heights after GH treatment in girls during the phGH and early rhGH periods. Reproduced with permission of the Japanese Society for Pediatric Endocrinology from Toshiaki Tanaka. History of GH treatment in Japan. Clin Pediatr Endocrinol 31: 5, 2022.
girls: \( r = 0.79, p < 0.01 \) : MPHD boys: \( r = 0.71, p < 0.01 \), girls: \( r = 0.97, p < 0.01 \), and age at the onset of puberty was positively correlated with age at the start of GH treatment in IGHD (boys: \( r = 0.67, p < 0.01 \); girls: \( r = 0.67, p < 0.01 \)). With regard to patient background, overall, 56% of the patients were born by breech delivery, and 44% of the patients had birth asphyxia. In the IGHD group (n = 108), 48% of the patients were born by breech delivery, and 35% had birth asphyxia. In the MPHD group (n = 26), 88% of the patients were born by breech delivery, and 73% had birth asphyxia. Both the rates were significantly higher. Hibi confirmed the “Birth injury theory”, explaining that disorders of the pituitary gland caused by breech delivery led to MPHD (11). Pituitary hypoplasia (12) and transection of the pituitary stalk (13, 14) were observed in patients with MPHD who were born by breech delivery, supporting this theory. In clinical practice, the number of patients with typical MPHD decreased as the mode of delivery changed from breech delivery to cesarean section.

The adult heights of phGH-treated patients who reached their adult heights from 1986 to 1989 were reported by Tanaka et al. in 2001 (7) (as Group P2 [late phGH period] in Fig. 4(a)(b)), demonstrating increased adult height in IGHD but decreased adult height in MPHD.

2) Adult height in the early rhGH period

A series of reports from the United States and the United Kingdom in 1985 showed that patients treated with phGH developed Creutzfeld–Jakob disease (15–17). At that time, as the practical use of mhGH and natural recombinant hGH (rhGH) began, there was a switch from phGH to mhGH and rhGH worldwide. In Japan, Somatonorm®, a mhGH, was approved for use in 1986. Genotropin®, a rhGH, was approved in 1988, followed by Norditropin® and Humatrope® in 1989, Saizen® in 1982, and Growject® in 1993. The dosage and administration of rhGH was 0.5 IU/kg/wk, which was subcutaneously injected in six to seven divided doses per week.

The period from 1988, when the unit dose of rhGH was IU/kg week, to 2000, when the unit dose of rhGH was changed to mg/kg/wk, was defined as the early rhGH period.

Tanaka et al. (7) analyzed the adult height in patients registered in the FGS and treated with hGH since 1986. The patients were divided into two groups: Group P2, in which phGH treatment was started and adult height was reached from 1986 to 1989, and Group R, in which rhGH treatment was started after 1989. Fig. 4 (a) and (b) show the mean adult heights in IGHD with rhGH monotherapy and MGH patients by sex from reports by Hibi et al. in 1989 (4) and Tanaka et al. in 2001 (7). Group P1 (early rhGH period) consisted of patients with IGHD and MGH, as reported by Hibi (4). Group P2 (late rhGH period) consisted of patients with IGHD and MPHD who were initiated on rhGH treatment, and Group R (early rhGH period) consisted of patients with IGHD and MPHD who were initiated on rhGH treatment, as reported by Tanaka (7).

MPHD is associated with hypogonadism, and the epiphyseal plate is not closed because of poor progression of bone age before replacement therapy with sex hormones or gonadotropins, during which hGH can be administered to increase height. Adult height in patients with MPHD is directly proportional to the age at the start of replacement therapy. The mean ages at the start of the replacement therapy for MPHD were 19.4, 16.9, and 14.9 yr in boys in Groups P1, P2, and R, respectively, and 18.5, 14.5, and 13.9 yr in girls, respectively. The age at the start of replacement therapy decreased with time, resulting in lower adult height. In the early phGH period, age at the start of replacement therapy was very high because adult height was emphasized, but later psychosocial issues due to delayed puberty were emphasized. Consequently, age at the start of replacement therapy decreased with time, and adult height decreased concomitantly.

The average adult height of IGHD patients has been increasing over time. Intramuscular injection of phGH was performed 2–3 times a week, whereas subcutaneous injection of rhGH was performed 6–7 times a week. Even though the dosage was maintained for one week, the therapeutic effect was greater when the number of injections was higher (18, 19). However, the greatest cause of improvement in adult height during this period was that the height SDS increased at the start of treatment. Fig. 5 shows the mean improvement in height SDS from the start of GH treatment to adult height. The early phGH period showed the greatest improvement. Specifically, an improvement of 1.9 SD on an average was observed in girls. However, an improvement of only approximately 1 SD was observed in the late phGH and early rhGH periods. Fig. 6 shows the mean height SDS at the start of treatment. In the early phGH period, the height SDS was in the –4 SD range, but in the late phGH period, it was in the –3 SD range, and in the rhGH period, it was in the –2 SD range. In other words, early initiation of treatment before short stature becomes severe is a major factor in the improvement of adult height.

However, there was a limitation in improving adult height because there was a height restriction in the FGS termination criteria that GH treatment should be terminated when the height is 160 cm for boys and 150 cm for girls in the phGH period. The height limitation was eliminated in 1992.

3) Adult height in the late rhGH period

In 2000, the unit of dose was changed from biological activity IU (international unit) to mg by weight, and rhGH potency was defined as 3 IU/mg. Therefore, the 0.5 IU/kg/wk dose should be 0.167 mg/kg/wk for GHD. The Japanese Society for Pediatric Endocrinology (JSPE) requested that the MHW increase the dose at
the time the unit was changed because the therapeutic dose in Japan was lower than those in Europe and the United States (20), and 0.175 mg/kg/wk was approved. Doses up to 0.3 mg/kg/wk was approved in the United States. When the WHO Expert Committee on Biological Standardization assigned multiple laboratories to measure the biological activity of 1 mg of WHO 88/624, the international standard, the average result was 3.39 IU/mg (range 3.13–3.69) (21). Therefore, the change in the unit from IU to mg suggests that the biological activity of rhGH was higher than that of the converted value.

After rhGH was approved, pharmaceutical companies selling rhGH began building a database through a post-marketing survey and by analyzing GH treatment. Data on adult height are frequently reported in analyses such as the International Cooperative Growth Study/Kabi International Growth Study (ICGS/KIGS) by Sumitomo Pharma - Pharmacia - Pfizer, which sold Genotropin®, and the Genetics and Neuroendocrinology of Short Nature International Study (GeNeSIS) by Eli Lilly, which sold Humatrope® (22–25).

A higher therapeutic effect was reported in patients with severe GHD compared with that in patients with moderate/mild GHD in terms of short-term growth rate (24, 26, 27) as well as improvement in adult height and height SDS (8, 10, 22, 24). Table 1 shows a comparison of adult height according to GHD severity. Age at the start of treatment tended to be lower in patients with severe GHD, although the difference was not necessarily significant among the reports. The height SDS at the start of treatment was lower in patients with severe GHD, and adult height was greater in both men and women. The improvement in height SDS from the start

---

**Fig. 5.** Comparison of improvement in the height SD scores after GH treatment in isolated GHD during the phGH and early rhGH eras.

**Fig. 6.** Changes in the incidence of severe GHD in cephalic and breech deliveries.
of GH treatment to the time of attaining adult height was significantly greater in patients with severe GHD in all the reports. There was no difference in the therapeutic effect between patients with moderate and mild GHD in terms of short-term growth rate (24, 26) or adult height (8, 10). This indicates that patients with mild GHD had a therapeutic effect similar to that of patients with moderate GHD.

**Table 1.** Comparison of adult height in idiopathic GHD patients with different severity after rhGH treatment in Japan

| Year | Author (Collaboration) | Sex | Severity | N     | At start of GH Age (yr) | Ht SDS (SD) | At adult height Height (cm) | Ht SDS (SD) | Increase in Ht SDS (SD) |
|------|------------------------|-----|----------|-------|-------------------------|-------------|----------------------------|-------------|------------------------|
| 1999 | Takano K (22) (KIGS)   | Males + Females | Severe | 31    | 10.4                    | −3.9*       | −1.35                      | 2.5*        |                       |
|      |                        |     | Moderate | 64    | 12.2                    | −2.8        | −1.35                      | 1.4         |                       |
| 2010 | Tanaka T (24) (KIGS)   | Males | Severe | 66    | 8.6*                    | −3.78*      | 163.4*                     | −1.22*      | 2.01*                  |
|      |                        |     | Moderate | 87    | 10.3                    | −3.00       | 160.6                      | −1.7        | 0.95                   |
|      |                        | Females | Severe | 51    | 8.0*                    | −3.59*      | 149.5*                     | −1.56*      | 1.48*                  |
|      |                        |     | Moderate | 83    | 8.9                     | −3.21       | 146.8                      | −2.05       | 0.91                   |
| 2011 | Fujieda K (10) (KIGS)  | Males | Severe | 59    | 10.49*                  | −3.68*      | 161.7                      | −1.55       | 2.13*                  |
|      |                        |     | Moderate | 97    | 12.11                   | −2.67       | 160.5                      | −1.75       | 1.22                   |
|      |                        |     | Mild     | 72    | 11.68                   | −3.16       | 159.6                      | −1.93       | 1.12                   |
|      |                        | Females | Severe | 33    | 10.32                   | −3.70       | 147.7                      | −2.04       | 1.66*                  |
|      |                        |     | Moderate | 78    | 10.72                   | −3.42       | 146.1                      | −2.37       | 0.94                   |
|      |                        |     | Mild     | 43    | 9.94                    | −3.16       | 147.4                      | −2.09       | 1.04                   |
| 2012 | Ogawa M (8) (SGOC)     | Males + Females | Severe | 11    | 9.0                     | −3.28       | −0.65                      | 2.63*       |                       |
|      |                        |     | Moderate | 41    | 9.3                     | −2.72       | −1.35                      | 1.37        |                       |
|      |                        |     | Mild     | 37    | 9.2                     | −2.66       | −1.32                      | 1.34        |                       |

KIGS, Kabi International Growth Study; SGOC, Study Group of Outpatient Clinic for Short Stature; Ht SDS, Height standard deviation score. * Significant difference from moderate and mild GHD.

**Table 2.** Adult height of idiopathic GHD patients after rhGH treatment in Japan

| Year | Author (Collaboration) | Sex | N     | mean GH dose | At start of GH Age (yr) | Ht SDS (SD) | At adult height Height (cm) | Ht SDS (SD) | Increase in Ht SDS (SD) |
|------|------------------------|-----|-------|--------------|-------------------------|-------------|----------------------------|-------------|------------------------|
| 1999 | Tanaka T (23) (KIGS)   | Males | 76    | 0.5 IU/kg/wk | 12.19                    | −2.78       | 162.5                      | −1.36       | 1.50                   |
|      |                        | Females | 52    |              | 11.57                    | −3.02       | 151.1                      | −1.34       | 1.73                   |
| 2001 | Tanaka T (28) (FGS)    | Males | 649   | NR           | 12.3                     | −2.68       | 160.3                      | −1.80       | 0.87                   |
|      |                        | Females | 552   |              | 11.0                     | −2.89       | 147.8                      | −2.03       | 0.54                   |
| 2010 | Tanaka T (24) (KIGS)   | Males | 153   | 0.184 mg/kg/wk | 9.6                      | −3.33       | 161.8                      | −1.49       | 1.41                   |
|      |                        | Females | 194   |              | 8.6                      | −3.36       | 147.8                      | −1.86       | 1.13                   |
| 2012 | Ogawa M (8) (SGOC)*    | Males | 31    | 0.192 mg/kg/wk | 9.37                     | −2.47       | 162.7                      | −1.39       | 1.09                   |
|      |                        | Females | 39    |              | 8.28                     | −2.68       | 151.3                      | −1.28       | 1.40                   |
| 2018 | Tanaka T (9) (SGOC)    | Males | 31    | NR           | 9.4                      | −2.47       | 162.8                      | −1.38       | 1.11                   |
|      |                        | Females | 39    |              | 8.4                      | −2.68       | 151.3                      | −1.28       | 1.42                   |
| 2020 | Tanaka T (25) (GeNeSIS)** | Males | 118   | M: 0.18 mg/kg/wk | 11.20                    | −2.82       | 159.3                      | −2.06       | 0.76                   |
|      |                        | Females | 95    | F: 0.17 mg/kg/wk | 10.02                    | −2.93       | 146.5                      | −2.18       | 0.75                   |

KIGS, Kabi International Growth Study; FGS, Foundation for Growth Science; SGOC, Study Group of Outpatient Clinic for Short Stature; GeNeSIS: Genetics and Neuroendocrinology of Short stature International Study. * Data calculated from original data. ** Data calculated from published data. NR: not reported.

Tanaka

doi: 10.1297/cpe.31.2022-0034
adult height was 159.3 cm to 162.8 cm (−2.06 SD to −1.36 SD) for boys and 146.5 cm to 151.3 cm (−2.18 SD to −1.28 SD) for girls, showing no trend of adult height increase over time, and the mean adult height SDS did not reach −1 SD. KIGS reported the largest improvement in height SDS in 1999. No trend of adult height improvement may be partly attributable to the decrease in the number of patients with severe GHD. The percentage of patients with severe idiopathic GHD was 25% in the report by Tanaka et al. (23) in 1999, but the percentage decreased to 12.4% in the report by Ogawa et al. (8) in 2012 and 9.3% in the report by Tanaka et al. (9) in 2018. Severe GHD is expected to continue to decrease in the future, and the challenge is to increase adult height in patients with moderate/mild GHD.

**Comparison of Adult Heights between Japanese and Americans or Europeans in the Late rhGH Period**

Table 3 shows the reports of adult height in patients with idiopathic GHD after rhGH treatment in Europe and the United States (29–34). According to many reports, adult height SDS had reached −1.0 SD in Europe and the United States. The differences in the adult heights of Japanese patients and patients in Europe and the United States with GHD after GH treatment were investigated (Table 2). One obvious factor was the difference in the therapeutic dose. In many countries, patients were treated with a higher therapeutic dose than that in Japan. As evident in the report by Radetti et al. (29), treatment using higher doses also resulted in greater improvements in height SDS from the start of treatment to adult height, and resulted in significantly greater adult height (Table 3). However, a report by Radatti et al. (29) on low-dose GHD treatment showed a similar situation as that in Japan, and reports by Magnhie et al. (30) and Rachemiel et al. (32) also showed that the adult height in GHD patients was approximately −1.0 SD. Early diagnosis and treatment have been recommended in Japan, and the age at the start of treatment has decreased, and height SDS has increased. However, GH treatment is expensive in Japan, and the subsidy system has a criterion of −2.5 SD or less. Therefore, the mean SDS for height at the start of treatment rarely exceeded −2.5 SD (Table 2). In Europe and the United States, there have been several reports of a mean height SDS of −2.5 to −2.0 at the start of treatment (Table 3).

Furthermore, in a report by Rachemiel (32), at 0.18 mg/kg/wk, improvement in height SDS from the start of GH treatment to adult height was +1.7 SD and +2.1 SD in men and women, respectively, showing an improvement of at least 1.5 SD. In contrast, in Japan, there have been no reports showing improvement in height SDS of 1.5 SD or higher, except for the report by Tanaka et al. in 1999 (23), in which patients with severe GHD accounted for 25%. This suggests that there are racial differences in the response to GH treatment.

### Limitation of GH Treatment in Japan

1) **Racial differences in the response to GH treatment**

As suggested above, racial differences in response to GH treatment were investigated. Tanaka (35) compared the improvement in growth rate and height SDS in the first year, adult height SDS, and improvement in height SDS up to adult height between two groups

---

**Table 3.** Adult height in idiopathic GHD patients after rhGH treatment in Western countries

| Year | Author | Country/Race | rhGH dose | Sex | Number | Age (yr) | Ht SDS (SD) | Adult Ht SDS (SD) | Increase in Ht SDS (SD) |
|------|--------|-------------|-----------|-----|--------|----------|-------------|-------------------|------------------------|
| 2003 | Radetti M (29) | Italy | 0.30 mg/kg/wk | M/F | 10/3 | 11.6 | −2.26 | −0.45 | 1.81 |
|      |        |            | 0.15 mg/kg/wk | M/F | 10/3 | 11.5 | −2.30 | −1.07 | 1.23 |
| 2006 | Magnhie M (30) | Italy | 0.17–0.21 mg/kg/wk | Males | 26 | 8.0 | −3.0 | −0.9 | 2.1 |
|      |        |            |            | Females | 13 | 7.7 | −2.6 | −0.4 | 2.3 |
| 2006 | Reiter EO (31) (KIGS) | Caucasian | 0.13–0.30 mg/kg/wk | Males | 351 | 10.1 | −2.4 | −0.8 | 1.6 |
|      |        |            |            | Females | 200 | 9.3 | −2.6 | −1.0 | 1.6 |
| 2007 | Rachmien M (32) | Canada | 0.18 mg/kg/wk | Males | 73 | 11.9 | −2.76 | −1.02 | 1.7 |
|      |        |            |            | Females | 23 | 11.8 | −3.19 | −1.07 | 2.1 |
| 2018 | Pfäffle R (33) (GeNeSIS) | USA | 0.33 mg/kg/wk | M+F | 587 | 11.0 | −2.13 | −0.79 | 1.34 |
|      |        |            | 0.20 mg/kg/wk | M+F | 398 | 9.6 | −2.33 | −0.88 | 1.45 |
|      |        |            | 0.25 mg/kg/wk | M+F | 242 | 11.0 | −2.28 | −0.98 | 1.3 |
| 2018 | Deal C (34) (GeNeSIS) | Canada | 0.20 mg/kg/wk | M/F | 33/17 | 11.4 | −2.7 | −1.07 | 1.63 |
|      |        |            | 0.25 mg/kg/wk | M/F | 1412/910 | 11.2 | −2.38 | −1.02 | 1.36 |

HtSDS, Height standard deviation score; KIGS. Kabi International Growth Study; GeNeSIS, Genetics and Neuroendocrinology of Short stature International Study. M, Male; F, Female.
whose age, height, height SDS, and dose of GH at the start of treatment did not differ between Japanese and Caucasian patients (Japanese: 56 boys, 60 girls; Caucasian: 142 boys, 96 girls) according to the KIGS analysis. The mean growth rate in the first year was 7.3 cm and 6.9 cm for Japanese boys and girls, respectively, and 7.9 cm and 8.2 cm for Caucasian boys and girls, respectively, showing a significantly higher growth rate in Caucasians. A significant difference was also observed in the improvement in the height SDS. The mean adult height SDS was −1.80 SD for Japanese boys and −2.09 SD for girls, being significantly lower than observed in the improvement in the height SDS. The results indicate that there are racial differences in the response to GH treatment, and that Japanese patients are less responsive than Caucasians.

2) Problems with the hGH therapeutic dose

GH treatment for GHD is referred to as replacement therapy. The replacement compensates for the deficiency in physiological amounts. Exogenously administered hGH inhibits endogenous GH secretion via negative feedback. Even at a dose of 0.175 mg/kg/wk, endogenous hGH secretion was mostly inhibited (36), indicating that exogenous hGH administration only plays a role in growth.

The clinical trial in GHD patients in Japan was only conducted at a single dose of 0.5 IU/kg/wk (0.167 mg/kg/wk); therefore, only this therapeutic dose was allowed. Catch-up growth was observed even at this therapeutic dose, and the treatment was approved based on 1–2-yr data. When the unit was changed in 2000, the current dose of 0.175 mg/kg/wk (25 μg/kg/d) was approved upon request from JSPE, claiming that the therapeutic dose in Japan was lower than that in foreign countries.

With respect to physiological GH secretion in children, Martha et al. (37) examined the hGH concentrations in blood collected every 20 min for 24 h in healthy boys and reported that the mean hGH secretion was 610 ± 65 μg (21 ± 2.0 μg/kg) in 11 prepubertal boys, 740 ± 110 μg (19 ± 3.1 μg/kg) in 12 early-pubertal boys, and 1810 ± 250 μg (35 ± 5.0 μg/kg) in 16 late-pubertal boys. Although the daily injection of GH is not equal to the physiological secretion, the dose was comparable to the physiological secretion amount of GH. The therapeutic dose of 0.175 mg/kg/wk (25 μg/kg/d) in Japan is slightly higher than the secretion during prepuberty, which is lower than the secretion during late puberty. It may be approximately equal to the secretion during middle puberty. The therapeutic dose of 0.30 mg/kg/wk (∼ 43 μg/kg/d) approved in the United States is purely a pharmacological dose.

However, is replacement therapy appropriate for GHD treatment? The clinical symptom of GHD is a decrease in the growth rate, and the expected improvement of symptoms with replacement therapy with a physiological amount of GH is the normal growth rate. At the early stage of treatment, however, catch-up growth continues for approximately 2 years, even with a physiological amount of GH. The bone seems to be more reactive, and catch-up growth presumably occurs because GH secretion is low before treatment. After 3 years, the growth rate is almost as high as that of healthy children. This phenomenon is called the waning phenomenon, but the author considers it to be the therapeutic effect of the original physiological amount administered in replacement therapy. Thus, the improvement in the height SDS is only approximately 1 SD in the first 2–3 years, the onset of puberty is also affected, which will be described later, and adult height improved by only by approximately 1 SD. This is the current situation of GHD in Japan.

When the therapeutic dose of rhGH approved worldwide for pediatric GHD is compared in terms of Humatrope®, the lowest single dose is used in Japan as shown in Table 4, but the range of therapeutic dose has been approved in other countries, with doses up to 0.30 mg/kg/wk allowed in the United States and Taiwan. The reason for the low therapeutic dose being used in Japan is the attitude of Japanese pharmaceutical companies that prevented them from properly conducting dose-finding studies.

3) Problems of the timing of pubertal onset

Another limitation is that hGH treatment may accelerate the onset of puberty. Pubertal development in GHD patients is slower than that in healthy children (38–40). Adult height in GHD patients is strongly and positively correlated with height at the onset of puberty (4, 41). To increase adult height, it is necessary to increase height at the onset of puberty as much as possible. If GH treatment is started early, patients will catch up to normal height early because they respond well to GH (42). If GH does not affect the onset of puberty, that is, if puberty starts at a similar age regardless of whether GH treatment was started early or late, the earlier the treatment was started, the greater the height at the onset of puberty. Thus, the adult height should be greater. However, recent reports in patients who started treatment at < 10 yr (8, 9, 25) indicate that the mean adult height in patients with idiopathic GHD after

| Table 4. Comparison of Humatrope® dose in GHD among countries |
|---------------------------------------------------------------|
| **Country** | **Dose** |
| Japan | 0.175 mg/kg/wk |
| USA | 0.18–0.30 mg/kg/wk |
| United Kingdom | 0.175–0.245 mg/kg/wk |
| France | 0.175–0.245 mg/kg/wk |
| Germany | 0.175–0.245 mg/kg/wk |
| Taiwan | 0.18–0.30 mg/kg/wk |
| Australia | 0.177–0.26 mg/kg/wk |

doi: 10.1297/cpe.31.2022-0034
rhGH monotherapy had not reached –1.0 SD, the mean improvement in the height SDS had not reached 1.5 SD, and poor improvement was seen in adult height (Table 2).

Tanaka et al. (43) examined each age at the onset of puberty by dividing 83 boys and 51 girls who started GH treatment for IGHD at a sufficiently younger age than the mean age at puberty (11.7 yr for boys and 11.4 yr for girls) into two groups by age at the start of treatment (younger than 10 yr for boys and 9 yr for girls). In both boys and girls, the groups that started treatment earlier entered puberty significantly earlier, and there was a significantly positive correlation between age at GH initiation and puberty onset. These results suggest that GH treatment may normalize late-onset puberty. As a result, puberty onset was at almost the same height, regardless of whether GH treatment was started early or late. This finding suggests that adult height, which is strongly correlated with height at the onset of puberty, is expected to be almost the same, suggesting that early treatment initiation does not lead to an improvement in adult height.

### Patients’ and Parents’ Expectations from GH Treatment

Statistically, because the normal height is –2.0 SD or more, the normal adult height is 159.1 cm for boys and 147.6 cm or more for girls. However, according to a questionnaire survey of preferred adult height, patients with short stature desire a minimum height of 160 cm for boys and 150 cm for girls, and about half of the boys with GHD who are undergoing GH treatment reported the desired height to be 170 cm, whereas the median desired height was 160 cm for girls, where almost all girls desired an average adult height (44), suggesting higher expectations from GH treatment. As a clinician treating GHD with GH, it may be practically difficult to achieve the desired height, but one’s personal thoughts and feelings are aimed to increase adult height as much as possible by treatment. The author hopes to achieve an adult height of at least 150 cm (–1.53 SD) for girls and 165 cm (–1.00 SD) or more for boys because boys’ parents are highly conscious of their son’s heights, and the percentage of children with short stature who visit the outpatient clinic for short stature is higher in boys (45).

However, as previously mentioned, currently, most Japanese patients with GHD are moderate and mild cases that are less responsive than patients with severe GHD, and only one dose, which is the lowest in the world, has been approved. Owing to the high cost of treatment, it is not possible to start treatment from an early stage for short stature due to the subsidy system, and the response to hGH is poor in terms of race. As such, there are some disadvantages.

### Treatments that Increase Growth During Puberty

If height at the onset of puberty cannot be increased despite initiating early GH treatment, improvement in adult height can be expected by increasing pubertal growth.

One approach is to increase GH dose during puberty. Stanhope et al. (46) conducted a prospective randomized trial in 32 children with GHD to determine whether an increase in the GH dose during puberty would improve adult height. At the onset of puberty, either an unchanged dose of 15 IU/m²/wk (0.15 mg/kg/wk) or a doubled dose of 30 IU/m²/wk (0.3 mg/kg/wk) was randomly assigned to each patient. The double dose of GH caused no significant change in height velocity during puberty. It was concluded that a higher dose shortened the duration of puberty without increasing adult height. Albertsson-Wikland et al. (47) also reported that the mean height SDS increase in boys with GHD was 0.7 SDS in the groups that received 0.7 IU/kg/wk (0.23 mg/kg/wk) and 1.4 IU/kg/wk (0.47 mg/kg/wk) in a once-daily injection during puberty. Doubling the GH dose during puberty did not increase height SDS during puberty.

Other approaches include gonadal suppression combination therapy (48–52) and anabolic hormone combination therapy (9, 25, 53), whose effects have been confirmed. Progression of bone age during puberty depends on sex hormones, and fusion of the epiphyseal plate is clinically proven in both boys and girls because of estrogen (54, 55). These methods aim to improve adult height by suppressing sex hormones to delay bone age progression and epiphyseal fusion and increase the duration of puberty.

The first combination therapy used for gonadal suppression used cyproterone acetate (48); subsequently, leuprolin acetate (Leuplin®), a gonadotropin-releasing hormone (GnRH) analog, was used. The suppression of sex hormones delays bone age progression, but decreases the growth rate. Therefore, it is important to maintain the growth rate with adequate rhGH levels. However, it is difficult to maintain a sufficient growth rate after the peak growth rate, especially in girls, and the concomitant use of rhGH and GnRH analogs for 3–4 years or longer is required to confirm the therapeutic effect (51, 52). GnRH analogs also suppress the maturation of secondary sexual characteristics.

Anabolic hormones that are not affected by aromatases are not metabolized to estrogens and, therefore, do not advance bone age. They inhibit gonadotropins as sex hormones by negative feedback action on the central nervous system. Consequently, testosterone levels decrease and bone age progresses slowly in boys (53, 56). Anabolic hormones (methenolone acetate [Premobolan®], currently available in Japan) have growth-promoting and secondary sexual characteristic-promoting effects like sex hormones; thus, it is easy to maintain sufficient growth rate and...
sexual maturation when used in combination with rhGH. However, because gonadotropins are suppressed, the increase in testicular volume was suppressed during treatment. In a report by Tanaka Growth Clinic, the mean growth at puberty in boys was 25.4 cm with rhGH monotherapy and 31.5 cm with concomitant therapy with anabolic hormones (53). Owing to the virilizing effect of anabolic hormones, it is difficult to use them in girls.

These treatment reports were not derived from prospective control studies and were not covered by health insurance.

**Prospects for Improving Adult Height**

In Japan, the conditions (1. therapeutic dose that enables sufficient catch-up from an early stage; 2. dose increase range, which allowed sustained catch-up; 3. good adherence to treatment, 4. high height at the onset of puberty and satisfactory height for adults, and 5. low-cost therapeutic dose) are desirable for future GH treatment.

In recent years, long-acting hGH (LAGH) has been developed and approved in Japan for the treatment of GHD in adults (57) and children (58). Patients and parents prefer once-weekly injections over daily injections (59). Reducing injection frequency improves patient adherence. In pediatric trial results with weekly injections, the mean growth rate after 1 year was greater than that with daily injections of 0.175 mg/kg/wk, depending on the therapeutic dose of LAGH. There were no significant adverse events other than the pain caused by the injection (58, 60). Although no long-term therapeutic effects have been reported, the effect on adult height is expected to be significant. Given the high expectations of children with GHD and their parents (56), future transitions from daily rhGH to LAGH can be expected if no adverse events occur during long-term use.

**Conflict of interests:** The author has received consulting fees/honoraria from JCR Pharmaceuticals.

---

### References

1. Tanaka T. History of GH treatment in Japan. Clin Pediatr Endocrinol 2022;31:1–9. [Medline] [CrossRef]

2. Tanaka T, Tachibana K, Shimatsu A, Katsumata N, Tsushima T, Hizuka N, et al. A nationwide attempt to standardize growth hormone assays. Horm Res 2005;64(Suppl 2):6–11. [Medline]

3. Tanaka T, Takano K, Hanew K, Nishi Y, Igarashi Y, Hirano T, et al. Registration system for growth hormone (GH) treatment with standardized immunoreactive GH values in Japan. Endocr J 1998;45:459–63. [Medline] [CrossRef]

4. Hibi I, Tanaka T and Committee for Treatment of Growth Hormone Deficient Children. Foundation of growth science: final height of patients with idiopathic growth hormone deficiency after long-term growth hormone treatment. Acta Endocrinol 1989;120:409–15. [CrossRef]

5. Tanaka T, Tachibana K, Hirano T. Report from Registration System Study Committee, The foundation for growth science. Annual Research Report 1996;20:1–18.

6. Isojima T, Hasegawa T, Yokoya S, Tanaka T. Demographic characteristics of children with growth hormone deficiency from 1996 to 2015 in Japan: 20 years of data from the foundation for growth science in Japan. Endocr J 2022;EJ21–0520.10.1507/endocrj. [Medline]

7. Tanaka T, Hanew K, Nishi Y, Tachibana K, Yokoya S, Igarashi Y, et al. Final height of growth hormone (GH)-treated short children registered at the Foundation for Growth Science in Japan: Comparison between the pituitary human GH era and the recombinant human GH era. Clin Pediatr Endocrinol 2001;10:53–62. [CrossRef]

8. Ogawa M, Nose O, Okada T, Kamijo T, Kinoshita E, Tokuda M, et al. Improvement of adult height in GH-treated idiopathic growth hormone deficiency. Jpn Pediatr Soc 2012;116:979–84 (in Japanese).

9. Tanaka T, Nakano Y, Nose O, Tokuda M, Kinoshita E, Tsuru N, et al. A 2016 survey on adult height after growth hormone treatment in patients with idiopathic growth hormone deficiency: Combination treatment with anabolic steroid hormone improves adult height in boys. J Jpn Hum Audo 2018;24:35–42.

10. Fujioka K, Tanaka T, Takano K, Chihara K, Seino Y, Irie M, KIGS Japan Scientific Committee. Adult height after growth hormone treatment in Japanese children with idiopathic growth hormone deficiency: analysis from the KIGS Japan database. J Pediatr Endocrinol Metab 2011;24:457–62. [Medline] [CrossRef]

11. Hibi I. The birth injury theory of “idiopathic” growth hormone deficiency. Clin Pediatr Endocrinol 1992;1:1–3. [CrossRef]

12. Inoue Y, Nemoto Y, Fujita K, Aoki Y, Takekage Y, et al. Pituitary dwarfism: CT evaluation of the pituitary gland. Radiology 1986;159:171–3. [Medline] [CrossRef]

13. Fujiiwa I, Kikuchi K, Nishimura K, Togashi K, Itoh K, Noma S, et al. Transection of the pituitary stalk; Development of an ectopic posterior lobe assessed with MRI imaging. Radiology 1987;165:486–9.

14. Kikuchi K, Fujisawa I, Momoi T, Yamanaka C, Kaji M, Nakano Y, et al. Hypothalamic-pituitary function in growth hormone-deficient patients with pituitary stalk transection. J Clin Endocrinol Metab 1988;67:817–23. [Medline] [CrossRef]

15. Koch TK, Berg BO, De Armond SJ, Gravina RF. Creutzfeldt-Jakob disease in a young adult with idiopathic hypopituitarism. Possible relation to the administration of cadaveric human growth hormone. N Engl J Med 1985;313:731–3. [Medline] [CrossRef]

16. Gibbs CJ Jr, Joy A, Heffner R, Franko M, Miyazaki M, Asher DM, et al. Clinical and pathological features and laboratory confirmation of Creutzfeldt-Jakob disease in a recipient of pituitary-derived human growth hormone. N Engl J Med 1985;313:734–8. [Medline] [CrossRef]
Adult height for Japanese GHD patients

doi: 10.1297/cpe.31.2022-0034
44. Naiki Y, Horikawa R, Tanaka T, Child Health and Development Network. Assessment of psychosocial status among short-stature children with and without growth hormone therapy. Clin Pediatr Endocrinol 2013;22: 25–32 (in Japanese). [Medline] [CrossRef]

45. Tanaka T, Soneda S, Sato N, Kishi K, Noda M, Ogasawara A, et al. The boy:girl ratio of children diagnosed with growth hormone deficiency-induces short stature is associated with the boy:girl ratio of children visiting short stature clinics. Horm Res Paediatr 2021;94: 211–8. [Medline] [CrossRef]

46. Stanhope R, Uruena M, Hindmarsh P, Leiper AD, Brook CGD. Management of growth hormone deficiency through puberty. Acta Paediatr Scand Suppl 1991;372(suppl): 47–52, discussion 53. [Medline] [CrossRef]

47. Albertsson-Wikland K, Alm F, Aronsson S, Gustafsson J, Hagenäs L, Häger A, et al. Effect of growth hormone (GH) during puberty in GH-deficient children: preliminary results from an ongoing randomized trial with different dose regimens. Acta Paediatri 1999;88(suppl): 80–4. [CrossRef]

48. Hibi I, Tanaka T, Tanae A, Kagawa J, Hashimoto N, Yoshizawa A, et al. The influence of gonadal function and the effect of gonadal suppression treatment on final height in growth hormone (GH)-treated GH-deficient children. J Clin Endocrinol Metab 1989;69: 221–6. [Medline] [CrossRef]

49. Tanaka T, Satoh M, Yasunaga T, Horikawa R, Tanae A, Hibi I. GH and GnRH analog treatment in children who enter puberty at short stature. J Pediatr Endocrinol Metab 1997;10: 623–8. [Medline] [CrossRef]

50. Tanaka T, Satoh M, Hibi I. Combined GH and LHRH analog treatment can increase pubertal growth in short children. Clin Pediatr Endocrinol 1997;6(suppl 9): 39–44. [CrossRef]

51. Tanaka T. Combination treatment of GH and LHRH analog to increase pubertal growth for GHD children who enter puberty with short stature. Clin Pediatr Endocrinol 2005;14(supple 24): S24_7–16. [CrossRef]

52. Tanaka T. Sufficiently long-term treatment with combined growth hormone and gonadotropin-releasing hormone analog can improve adult height in short children with isolated growth hormone deficiency (GHD) and in non-GHD short children. Pediatr Endocrinol Rev 2007;5: 471–81. [Medline]

53. Tanaka T, Sato N, Ogasawara A, Noda M, Naiki Y, Horikawa R. The effects of combination treatment of growth hormone and anabolic steroid hormone on adult height in boys with growth hormone deficiency. J Jpn Ass Hum Auxo 2017;23: 21–30.

54. Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 1994;331: 1056–61. [Medline] [CrossRef]

55. Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab 1995;80: 3689–98. [Medline]

56. Naiki Y, Ito M, Yoshimura K, Sato M, Ikema N, Horikawa R, et al. Growth promotion effect of an anabolic steroid on boys in puberty Jpn J. Dev Pharmacol Ther 2005;18: 143–6 (in Japanese).

57. Otsuka F, Takahashi Y, Tahara S, Ogawa Y, Hajby Rasmussen M, Takano K. Similar safety and efficacy in previously treated adults with growth hormone deficiency randomized to once-weekly somapacitan or daily growth hormone. Clin Endocrinol (Oxf) 2020;93: 620–8. [Medline] [CrossRef]

58. Horikawa R, Tanaka T, Hasegawa Y, Yorifuji T, Ng D, Rosenfeld RG, et al. Efficacy and safety of once-weekly somatrotropin compared with once-daily somatropin (Genotropin®) in Japanese children with pediatric growth hormone deficiency: results from a randomized phase 3 study. Horm Res Paediatr 2011;10.1159/000524600. [Medline]

59. Tanaka T, Sato T, Yuasa A, Akiyama T, Tawseef A. Patient preferences for growth hormone treatment in Japanese children. Pediatr Int 2021;63: 1185–91. [CrossRef]. [Medline]

60. Sävendahl L, Battelino T, Brod M, Hajby Rasmussen M, Horikawa R, Juul RV, et al. REAL 3 study group. Once-weekly somapacitan vs daily GH in children with GH deficiency: Results from a randomized phase 2 trial. J Clin Endocrinol Metab 2020;105: e1847–61. [Medline] [CrossRef]