An observational study of the effectiveness and safety of growth hormone (Humatrope®) treatment in Japanese children with growth hormone deficiency or Turner syndrome

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Abstract. This study assessed the effectiveness and safety of growth hormone (GH; Humatrope®) therapy in Japanese children with GH deficiency (GHD) or Turner syndrome (TS) enrolled in the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS). GeNeSIS is an open-label, multinational, multicenter, observational study conducted in 30 countries. In this interim report, there were 1129 GH treatment-naïve children with GHD, with a mean chronological age (± standard deviation) of 8.75 (3.32) years, and 90 girls with TS, with a mean chronological age of 8.93 (3.67) years. The mean height standard deviation score (SDS) increased from -2.73 (0.63) SD and -2.71 (0.63) SD at study entry to -2.22 (0.68) SD and -2.20 (0.60) SD after 1 year of treatment in the GHD and TS groups, respectively. In both groups, mean height SDS increased further with each year of treatment to 4 years; however, the magnitude of change in height SDS declined with time. The mean insulin-like growth factor-I SDS increased from below the mean of the reference population at study entry to a level similar to (GHD group) or higher than (TS group) the mean of the reference population during the 4-year treatment period. The incidence of serious adverse events (AEs), treatment-related AEs, and AEs related to glucose intolerance was low in both groups (0.1% to 3.0%). In conclusion, GH treatment in Japanese children with GHD or TS resulted in increased growth over a 4-year treatment period with a favorable safety profile; however, the improvements in growth declined with time.

Key words: Growth hormone, Growth hormone deficiency, Turner syndrome

STUDIES of growth hormone (GH) for short stature have been conducted predominantly in Caucasian patients, with fewer studies conducted in Japanese patients with growth hormone deficiency (GHD) or Turner syndrome (TS). The response to GH may differ in Japanese pediatric patients because of differences in ethnicity, clinical practice, and regulatory guidelines between Japan and other countries. The Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) is a multinational, multicenter, observational, post-marketing study to evaluate the long-term safety and effectiveness of GH (Humatrope®, Eli Lilly and Company, Indianapolis, USA) therapy in pediatric patients. This manuscript reports the interim effectiveness and safety data of GH from the GeNeSIS study in Japanese children with short stature associated with GHD or TS.
Materials and Methods

Study information

GeNeSIS is an open-label, multinational, multicenter, observational study conducted in 30 countries, including Japan (ClinicalTrials.gov Identifier: NCT01088412). This interim report describes the results for Japanese patients enrolled from July 1999 to June 2008. The study was conducted in accordance with the Declaration of Helsinki, with approval from participating institutional ethics review boards. Written informed consent was required from the parents or legal guardians of the pediatric patients.

Study design

Patients diagnosed with GHD or TS (based on the criteria from the Study Group of Hypothalamus-Pituitary Disorders, funded by the Japanese Ministry of Health, Labour and Welfare [1]) were enrolled. Complete GHD was defined as a GH peak concentration of ≤ 5 ng/mL and partial GHD as a GH peak concentration of > 5 ng/mL to ≤ 10 ng/mL. Height was recorded at study entry and the 6-monthly study visits. Laboratory data and bone age were collected at each visit, if available.

Study objectives

The aim of the study was to assess the effectiveness and safety of long-term GH use in pediatric patients. Efficacy outcomes included height standard deviation score (SDS), height velocity (HV), HV SDS, and insulin-like growth factor-I (IGF-I) SDS. Safety outcomes included the frequency and nature of treatment-related adverse events (AEs), serious adverse events (SAEs), and AEs related to glucose intolerance. The relationship between GH treatment and AEs was assessed by the primary doctor.

Statistical analysis

Efficacy outcomes were evaluated in patients with GHD or TS who were evaluable for efficacy, treatment-naïve at study entry, received GH treatment, and had height SDS data available at study entry and the 1-, 2-, 3-, and 4-year time points. Safety outcomes were evaluated in all patients enrolled in the study in Japan. All variables were summarized using descriptive statistics. Data are presented as the mean (± standard deviation [SD]), unless otherwise stated. Height SDS and HV SDS were calculated according to published standards for Japanese children [3, 4], and IGF-I SDS and IGF binding protein-3 (IGFBP-3) SDS were calculated according to published standards for healthy individuals [5, 6]. Statistical analyses were conducted using SAS software, Version 8.02 (SAS Institute, USA).

Results

Patient characteristics

In Japan, 1548 patients with short stature were enrolled in GeNeSIS: 1397 (90.2%) had GHD; 90 (5.8%) had TS; 57 (3.7%) had other causes of short stature; and the cause was unknown in 4 patients. The majority of patients were prepubertal at study entry: 92.3% of boys (704/763) were Tanner stage G1 and 88.5% of girls (478/540) were Tanner stage B1.

For the 1129 patients with GHD who were treatment-naïve at study entry, 62.6% were male and the mean chronological age was 8.75 (3.32) years (range 0.5, 17.1 years; Table 1). The age distribution at study entry tended to show two peaks (5, 11 years) for both the GHD and TS groups (Fig. 1). The height parameters at study entry indicated that the GHD and TS groups were shorter and had a slower growth rate than the reference population (Table 1).

The cause of GHD was idiopathic in the majority of patients (914/981, 93.2%). Of the 67 (6.8%) patients with organic GHD, 34 (50.7%) had congenital GHD and 33 (49.3%) had acquired GHD (9 of whom also had germinoma). Complete GHD was present in 260/921 patients (28.2%) and partial GHD in 519/921 patients (56.4%). Of the patients with organic GHD, 52.2% (35/67) also had a deficiency in TSH, 28.4% (19/67) in FSH, 34.3% (23/67) in cortisol/ACTH, 23.9% (16/67) in antidiuretic hormone, 13.4% (9/67) in prolactin, and 4.5% (3/67) in LH.

Treatment dose and duration

The mean average dose of GH and mean treatment duration were 0.19 mg/kg/week and 3.03 years, respectively, in the GHD group and 0.33 mg/kg/week and 3.04 years, respectively, in the TS group (Table 2). The mean starting, cessation, and average doses of GH were similar between boys and girls in the GHD group,
Effectiveness and safety of growth hormone

As were the mean total treatment duration and time to onset of puberty (Table 2).

Effects of GH on height parameters

In the GHD group, mean height SDS increased each year during the 4 years of treatment (Fig. 2A). However, the magnitude of change in height SDS declined with each successive year (Fig. 2B). The effect of treatment varied with GHD severity, with initially greater mean changes in height SDS observed in patients with complete GHD than those with partial GHD (Fig. 3). Effects on mean height SDS were also greater in the first year compared with subsequent years in the TS group (Fig. 4A, 4B).

In the GHD group, the mean HV and mean HV SDS were 4.68 (1.43) cm/year and -1.30 (1.23) SD, respectively, before treatment, and these values increased to 8.24 (1.86) cm/year and 2.09 (1.57) SD, respectively, after 1 year of GH treatment (Fig. 2C, 2D). A similar pattern was observed in the TS group. The mean HV and mean HV SDS were 4.14 (1.09) cm/year and -1.69 (0.71), respectively, before treatment, and these val-

Table 1 Characteristics of patients with GHD and TS at study entry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GHDa</th>
<th>TSb</th>
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<tbody>
<tr>
<td></td>
<td>All (n)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>CA (years)</td>
<td>962</td>
<td>8.75 (3.32)</td>
</tr>
<tr>
<td>BA (years)</td>
<td>544</td>
<td>6.25 (3.15)</td>
</tr>
<tr>
<td>BA – CA (years)</td>
<td>544</td>
<td>-2.34 (1.16)</td>
</tr>
<tr>
<td>Height SDS</td>
<td>980</td>
<td>-2.80 (0.61)</td>
</tr>
<tr>
<td>HV (cm/year)</td>
<td>923</td>
<td>4.84 (2.50)</td>
</tr>
<tr>
<td>HV SDS</td>
<td>922</td>
<td>-1.50 (3.26)</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>855</td>
<td>-1.11 (1.25)</td>
</tr>
<tr>
<td>IGFBP-3 SDS</td>
<td>430</td>
<td>-1.42 (3.00)</td>
</tr>
</tbody>
</table>

BA, bone age; CA, chronological age; GHD, growth hormone deficiency; HV, height velocity; IGF, insulin-like growth factor; IGFBP, IGF binding protein; SD, standard deviation; SDS, standard deviation score; TS, Turner syndrome. aPatients with GHD who were treatment-naive at study entry only. bPatients with TS were treatment-naive or receiving GH treatment at study entry.

Fig. 1 Distribution of chronological age at enrollment in the GHD (A) and TS groups (B)

CA, chronological age; GHD, growth hormone deficiency; TS, Turner syndrome
Table 2  GH treatment dose and duration

<table>
<thead>
<tr>
<th>Variable</th>
<th>GH treatment dose (mg/kg/week)</th>
<th>Duration of GH treatment (years)</th>
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<tbody>
<tr>
<td></td>
<td>Starting</td>
<td>Cessation</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>GHD</td>
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<tr>
<td></td>
<td>Boys</td>
<td>592</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>373</td>
</tr>
<tr>
<td>TS</td>
<td>All</td>
<td>69</td>
</tr>
</tbody>
</table>

GHD, growth hormone deficiency; SD, standard deviation; TS, Turner syndrome

Fig. 2  Treatment effect of GH over 4 years on height SDS (A), Δ height SDS (B), HV (C), and HV SDS (D) in the GHD group
The mean values are shown above the plots. GHD, growth hormone deficiency; HV, height velocity; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation; SDS, standard deviation score
Fig. 3  Treatment effect of GH over 4 years on Δ height SDS by severity of GHD (complete GHD, partial GHD, and all patients) GHD, growth hormone deficiency; SDS, standard deviation score

Fig. 4  Treatment effect of GH over 4 years on height SDS (A), Δ height SDS (B), HV (C), and HV SDS (D) in the TS group
The mean values are shown above the plots. HV, height velocity; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation; SDS, standard deviation score; TS, Turner syndrome
related to glucose intolerance, of which 2 AEs were considered related to GH (diabetes mellitus, increased glycosylated hemoglobin); the relatedness was not known for 2 AEs (hyperglycemia, glucose present in the urine). Two patients had an oral glucose tolerance test. In the TS group, 1 patient experienced type 2 diabetes mellitus (not considered related to GH).

Discussion

In this large-scale study, GH treatment was effective in increasing height in Japanese children with GHD or TS, and had a favorable safety profile. The results reported here are broadly consistent with published studies [7-14].

After 3 years of treatment, 69/379 patients (18.2%) in the GHD group and 11/34 patients (32.4%) in the TS group had an IGF-1 SDS over 2.0 SD; 49/379 (12.9%) and 8/34 (23.5%) patients had an IGF-1 SDS over 2.5 SD in the GHD and TS groups, respectively.

Safety

In the safety population (N = 1548), 45 patients (2.9%) in the GHD group reported 54 treatment-related AEs; the two most frequently reported were joint pain (18 cases, 12 patients) and hypothyroidism (6 cases, 6 patients). Twenty patients (1.3%) reported 30 SAEs, most frequently pneumonia (4) and craniopharyngioma (2); 4 SAEs were considered related to GH (craniopharyngioma, neurofibroma, scoliosis, diabetes mellitus). There were 2 treatment-related adverse events reported by 2 patients (0.1%) in the TS group: (proteinuria, scoliosis). One patient (0.1%) reported an SAE (tympanic membrane perforation, not considered related to GH).

In the GHD group, 7 patients experienced an AE related to glucose intolerance, of which 2 AEs were considered related to GH (diabetes mellitus, increased glycosylated hemoglobin); the relatedness was not known for 2 AEs (hyperglycemia, glucose present in the urine). Two patients had an oral glucose tolerance test. In the TS group, 1 patient experienced type 2 diabetes mellitus (not considered related to GH).
was relatively low in both the GHD and TS groups. The most frequently reported treatment-related AE was joint pain, a known side effect of GH related to its ability to stimulate growth [21]. There were two neoplasms considered related to GH. Extensive monitoring of the safety of GH therapy has revealed no increase in the incidence of de novo cancer or leukemia in patients without risk factors and no evidence that GH treatment increases the risk of tumor recurrence in patients successfully treated for their primary lesion [19, 20, 22, 23]. However, patients at high risk of developing a neoplasm should be monitored. Two patients reported AEs related to glucose intolerance that were considered related to GH. Growth hormone may decrease insulin sensitivity, particularly at higher doses in susceptible patients, leading to unmasking of previously undiagnosed impaired glucose tolerance and overt diabetes mellitus [19, 20, 24, 25].

The observational study design of GeNeSIS allowed evaluation of GH in real-world clinical practice. The large number of patients enrolled allowed detection of infrequently occurring AEs; however, the number of patients with TS was small, in particular, the number with 4-year data. In addition, GHD is a rare childhood disorder, making it difficult to conduct a large-scale study. However, as there are very strict criteria for GHD that must be fulfilled to receive GH treatment in Japan [26], the diagnosis of GHD in this study is expected to be accurate. The best measure of the overall effectiveness of GH in treating short stature is adult height; however, sufficient adult height data are not currently available in this study.

In conclusion, GH treatment in patients with GHD or TS resulted in increased growth, although the improvements tended to decline with time. Insulin growth factor-I levels were normalized in the GHD group and elevated in the TS group. Future investigations will report long-term effectiveness data, such as adult height, and further long-term safety data, including the incidence of neoplasms and glucose intolerance.

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Role of the sponsor
Eli Lilly was involved in the study design, data collection, and preparation of the manuscript. Following collection of the case report forms and translation of the text describing the adverse events into English, all data were transferred to a Kendle International (Netherlands) for analysis.

Role of contributors
All authors were involved in the study design and participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript.

Conflicts of interest
All authors have consulted for and/or participated in advisory panels for Eli Lilly.

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