Clinical trials of GH treatment in patients with Turner’s syndrome in Japan – a consideration of final height

K Takano1,6, M Ogawa2,6, T Tanaka3,6, K Tachibana4,6, K Fujita5,6, N Hizuka1,6 and The Members of the Committee for the Treatment of Turner’s Syndrome

1Department of Medicine, Institute of Clinical Endocrinology, Tokyo Women's Medical College, Tokyo 162, Japan, 2Department of Pediatrics, Nagoya University, Nagoya 466, Japan, 3National Children's Hospital, Tokyo 154, Japan, 4Kanagawa Children's Medical Center, Kanagawa 232, Japan, 5Department of Pediatrics, Osaka-City General Hospital, Osaka 534, Japan and 6The Foundation for Growth Science in Japan, Tokyo 162, Japan

(Correspondence should be addressed to K Takano, Department of Medicine, Institute of Clinical Endocrinology, Tokyo Women's Medical College, Tokyo 162, Japan)

Abstract

Clinical trials of human GH (hGH) therapy in Turner’s syndrome were started in 1986. Between 1986 and 1990, 362 patients were enrolled; 115 were treated for more than 6 years. The age at the start of treatment ranged from 5 to 18 years (mean 10 years). Fifty-one patients received hGH at a weekly dosage of 0.5 IU/kg and 64 received 1.0 IU/kg by daily s.c. injection. Both treatment groups showed a statistically significant growth increase during the initial 4 years of treatment. The rate of increase in height was significantly greater for the initial 2 years with the high dose than with the low dose. The increases in height over 6 years of treatment (expressed by S.D. score for chronological age) were 1.48 ± 0.8 with 0.5 IU/kg per week and 1.80 ± 1.0 with 1.0 IU/kg per week. To date, 260 patients have stopped GH therapy. In 32% of them, the height attained was above the −2 S.D. value for normal girls. In 27%, the growth rate was not sufficient when they stopped treatment. The mean final height (growth rate > 1.0 cm/year) of patients treated for more than 6 years was 142.2 ± 6.5 cm (n = 15) with 0.5 IU/kg per week, and 144.3 ± 3.9 cm (n = 15) with 1.0 IU/kg per week. The adult height was improved by GH treatment, although final height did not differ statistically between the two dose regimens. No remarkable adverse events occurred during the treatment. These results indicate that hGH treatment improves the final height in patients with Turner’s syndrome.

European Journal of Endocrinology 137 138–145

Introduction

Turner’s syndrome is a chromosomal disorder of females involving many physical abnormalities; it includes short stature and slow growth rate. Short stature has been treated with anabolic steroids, low doses of oestrogen, human growth hormone (hGH), or a combination therapy (1–5). Since the successful synthesis of hGH by recombinant DNA technology (6), several investigators have reported the safety and biological activity of recombinant hGH (rhGH) in humans. hGH therapy in Turner’s syndrome began systematically several years ago as clinical trials (7–11). Although GH could obviously induce a substantial increase in the rate of increase in height, the long-term outcome in terms of final height is still unclear. Final height data have been requested by the regulatory authority to validate the benefits of GH therapy in Turner’s syndrome.

The Japanese multicentre trial of GH therapy in Turner’s syndrome was started in 1986, and interim results have been reported (8, 12–16). In 1991, the Japanese Ministry of Health and Welfare approved GH treatment only for those patients with Turner’s syndrome who had GH deficiency, using a dose of 0.5 IU/kg per week which was the same as that given to patients with GH deficiency (pituitary dwarfism). Some of our patients who fulfilled these criteria were transferred to treatment with GH preparations which became commercially available at that time. Here, we report the results of clinical trials started between 1986 and 1990 in Japan. Most of the patients were included among those reported previously (8, 12–16). We performed the last survey of our clinical trials between May and August in 1996.

Subjects and methods

The number of patients enrolled in the clinical trials of GH treatment from 1986 to 1990 was 362. The criteria for the acceptance into these clinical trials were: sex chromosome analysis indicative of Turner’s syndrome; birth body weight more than 2000 g; chronological age more than 5 years; body height less than −2 S.D. of that
of age-matched normal girls; bone age less than 11 years old; and no previous therapy to accelerate the growth rate. Informed consent was obtained from each patient and her parents, and the experimental protocol was approved by the Human Subjects Investigation Committee of the participating medical hospitals. One hundred and eighty-six patients were treated with hGH 0.5 IU/kg per week and 176 were treated with 1.0 IU/kg per week. There were no differences among the groups in chronological age, bone age, height, degree of overweight and growth rate at the start of treatment. Their chronological age ranged from 5 to 18 years (mean 10.0 years; Fig. 1). The weekly dosage was divided into six or seven aliquots and was injected s.c. Vital signs, height and body weight were checked during the treatment, and blood count, urine analysis and laboratory tests including oral glucose tolerance were performed throughout treatment. During the first 3 years, the clinical trials were under the sponsorship of the pharmaceutical company which supplied hGH, but they subsequently came under the control of the Foundation for Growth Science in Japan. Combined oestrogen therapy was not allowed during the first 3 years of clinical trials. Thereafter, oestrogen therapy was started according to the wishes of the individual girl or to the advice of doctors. There is no standard for oestrogen therapy in patients with Turner’s syndrome in Japan, but they generally start therapy to induce puberty at about 16 years of age, compared with the age of about 13 years in their European counterparts. The drugs commonly given are conjugated oestrogen (Premalin 0.625–1.25 mg), mestranol (Devocin 0.02 mg), oestriol (Estriel 0.2 mg) and mixtures of oestrogen and progesterone (Duoluton, Sophia). During the 6 years of treatment received by 115 patients, 21 of them were treated with oestrogen and 40 did not receive any oestrogen therapies, even though they did not show any secondary sexual characteristics after the age of 13 years.

Growth hormone preparations used in this study were recombinant methionine-free hGH which was kindly provided by Sumitomo Pharmaceutical Co., Ltd (Osaka, Japan), Novo Nordisk Pharmaceuticals, Ltd (Tokyo, Japan) and Eli Lilly Japan K K (Kobe, Japan). Height s.d. score (SDS) and growth rate (SDS) were calculated using the data obtained from Japanese girls with Turner’s syndrome described previously (15). The
The mean height of Japanese patients with Turner's syndrome was 138 cm. Final height was defined here as a linear growth velocity of 1.0 cm/year or less.

For statistical analysis, parametric tests were used because the data fitted a normal distribution. The paired t-test was used to compare treatment results with baseline in each treatment group. Results are expressed as the mean ± S.D. Intergroup comparisons were performed with the unpaired t-test. Correlations between various measurements were calculated by linear regression analysis (Pearson's correlation coefficient). Differences with values of P < 0.05 were considered statistically significant.

Results

The periods of GH treatment received by the patients are shown in Table 2. During the first, second and third years of GH treatment, 14%, 20% and 16% respectively of the patients (50% over 3 years) withdrew from our clinical trials. The number of the patients did not differ statistically between the two dose groups. Thereafter, about 5–6% of the patients per year stopped treatment in both groups of patients. A total of 115 patients were treated for more than 6 years.

The growth rates of these 115 patients treated with GH are shown in Table 1. Fifty-one and 64 patients were treated with GH 0.5 IU/kg per week and 1.0 IU/kg per week respectively for more than 6 years. Both treatment groups showed a statistically significant increase in growth rate during the initial 4 years of treatment. The rate of increase in height was significantly greater for the initial 2 years in the high-dose group than in the low-dose group (P < 0.05). The height increase (expressed by SDS score) during 6–9 years of treatment is shown in Fig. 3. The increase in height (expressed by SDS score) during treatment was 1.48 ± 1.08 with 0.5 IU/kg per week and 1.80 ± 1.18 with 1.0 IU/kg per week (not statistically different). During 6–9 years of treatment (that statistically had spontaneous adrenarche and 17 of them had menarche), 4 patients showed a statistically significant increase in height.

Table 1 Growth rate (cm/year and ±S.D.) and change in growth rate (ΔSDS) before and during 6 years of treatment with hGH. Values are means ± S.D.

<table>
<thead>
<tr>
<th>GH 0.5 IU/kg per week (n = 51)</th>
<th>Before</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>cm/year</td>
<td>4.0 ± 1.1</td>
<td>5.9 ± 1.1*</td>
<td>4.6 ± 1.0*</td>
<td>4.0 ± 1.3</td>
<td>3.7 ± 1.2</td>
<td>2.8 ± 1.1*</td>
<td>2.6 ± 1.3*</td>
</tr>
<tr>
<td>S.D.</td>
<td>0.16 ± 1.22</td>
<td>2.51 ± 1.25*</td>
<td>1.16 ± 1.23*</td>
<td>0.78 ± 1.17*</td>
<td>0.80 ± 1.39*</td>
<td>0.60 ± 1.31</td>
<td>-0.09 ± 1.22</td>
</tr>
<tr>
<td>ΔSDS</td>
<td>0.016 ± 1.73</td>
<td>0.97 ± 1.77</td>
<td>0.72 ± 1.55</td>
<td>0.74 ± 1.88</td>
<td>-0.06 ± 1.94</td>
<td>-0.23 ± 1.86</td>
<td></td>
</tr>
<tr>
<td>GH 1.0 IU/kg per week (n = 64)</td>
<td>3.8 ± 1.0</td>
<td>7.0 ± 1.2*†</td>
<td>5.2 ± 1.1*†</td>
<td>4.5 ± 1.0*†</td>
<td>3.8 ± 1.4</td>
<td>3.1 ± 1.3*</td>
<td>2.9 ± 1.5*</td>
</tr>
<tr>
<td>cm/year</td>
<td>-0.18 ± 0.91</td>
<td>3.57 ± 1.42*†</td>
<td>1.27 ± 1.27*†</td>
<td>1.91 ± 1.21*†</td>
<td>0.69 ± 1.45*</td>
<td>0.23 ± 1.36*</td>
<td>0.27 ± 1.41*</td>
</tr>
<tr>
<td>S.D.</td>
<td>0.37 ± 1.75†</td>
<td>1.90 ± 1.73†</td>
<td>1.39 ± 1.63†</td>
<td>0.90 ± 1.78</td>
<td>0.43 ± 1.69</td>
<td>0.50 ± 1.81†</td>
<td></td>
</tr>
</tbody>
</table>

* P < 0.05 compared with before treatment; †P < 0.05 between two dosages.
their GH treatment. Data for these patients were analysed according to the age and growth rate when treatment terminated (Table 2). Among the 130 patients younger than 15 years, 52 treated with GH 0.5 IU/kg per week and 38 treated with 1.0 IU/kg per week (69.2% of the age group) stopped GH treatment in spite of a good growth rate of more than 4 cm/year, which is the mean growth rate of 8–9 year old patients with Turner’s syndrome. In 33 of the 130 patients (25.4%) younger than 15, the height attained when they stopped GH treatment was above the −2 S.D. value for normal girls. In contrast, 65 of the 130 patients (50%) older than 15 years stopped GH treatment in spite of a good growth rate of more than 2 cm/year. In 49 of the 130 patients (37.7%) older than 15, the height attained was above the −2 S.D. value for normal girls. Thus 70 of the 260 patients who stopped treatment (26.9%) were assumed to have stopped their GH treatment because of poor growth rates.

We analysed the data of patients who reached final adult height (growth rate ≤ 1 cm/year). Forty-five patients fulfilled this criterion; their ages ranged from 14 to 22 years, the duration of their treatment was 1 to 9 years and their heights ranged from 128.0 to 152.1 cm (Fig. 6). To study the effect of GH treatment on final adult height, we analysed the data of patients who were treated for more than 6 years. The height of the patients treated with GH 0.5 IU/kg per week ranged from 128.0 to 152.1 cm (mean 142.2 ± 6.5 cm, n = 15); that of patients treated with 1.0 IU/kg per week ranged from

![Figure 3](image-url) Individual height increase (ΔSDS) during 6–9 years of hGH treatment with 0.5 IU/kg per week (upper panel, n = 51) and 1.0 IU/kg per week (lower panel, n = 64). ●, Puberty (-); ○, spontaneous puberty (+); □, oestrogen-treated.

![Figure 4](image-url) Height of the patients before (left panel) and after (right panel) 6–9 years of 0.5 IU/kg per week hGH treatment (n = 51) plotted on growth curves for normal girls and girls with Turner’s syndrome. ●, Puberty (-); ○, spontaneous puberty (+); □, oestrogen-treated.
137.8 to 150.5 cm (mean 144.3 ± 3.9 cm, n = 15). These two mean values did not differ statistically. The heights did not differ among the four groups of patients of different pubertal status (Fig. 7). The mean height increase (ΔSDS) was 1.40 ± 0.89 and 1.40 ± 0.73 in groups treated with GH 0.5 IU/kg per week and 1.0 IU/kg per week respectively (difference not statistically significant; Fig. 8). The height increases did not differ among the four groups of different pubertal status.

We studied the factors which influenced the final height of these patients (n = 45). There were no correlations between the effect of GH expressed by final height (cm) and height increase (ΔSDS) on the one hand and the chronological age, bone age, height (cm), growth rate (cm/year, SDS) and overweight (%) at the start of GH treatment on the other. There was a slight correlation between height (SDS) at the start of GH treatment on the one hand and final height (r = 0.46, P<0.001), and height increase (ΔSDS) (r = 0.43, P<0.03) on the other. There were no correlations among the effect of GH and the dose of hGH used, growth rate during the first year of treatment and the duration of GH treatment.

During the GH treatment, plasma IGF-I levels increased to similar values in both groups of patients. Basal glucose and immunoreactive insulin levels increased slightly during the treatment, however, glucose intolerance was not observed during the treatment. Haemoglobin A1 levels were all within the normal range. There were no significant changes in blood count, urine analysis or routine biochemical data during the treatment.

Table 2 Height and growth rate at the termination of GH treatment. Values are number (%) of patients who fulfilled the criteria.

<table>
<thead>
<tr>
<th>GH (IU/kg per week)</th>
<th>Chronological age &lt;15 years</th>
<th>Chronological age ≥15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GR ≥ 4 cm/year</td>
<td>GR &lt; 4 cm/year</td>
</tr>
<tr>
<td>CH &lt; −2 s.d.</td>
<td>90 (100)</td>
<td>40 (100)</td>
</tr>
<tr>
<td>CH ≥ − 2 s.d.</td>
<td>26 (68)</td>
<td>14 (93)</td>
</tr>
<tr>
<td>Total</td>
<td>38 (100)</td>
<td>25 (100)</td>
</tr>
</tbody>
</table>

GR, Growth rate; CH, current height. * s.d. of normal girls of the same chronological age.
Discussion

Growth hormone treatment in patients with Turner’s syndrome has become widespread since adequate amounts of recombinant hGH became available. In Japan, we started clinical trials of hGH treatment in 1984, using recombinant methionyl-hGH (met-hGH) (7). We observed a growth promoting effect with met-hGH, but the production of antibody against hGH was observed in 50% of the patients. In the meantime, methionine-free recombinant hGH became available. We then started a multicentre trial of GH using the methionine-free hGH. As we reported previously, this GH had very low antigenicity, not only in patients with GH deficiency, but also in those with Turner’s syndrome. We published several papers on the effect of GH treatment in girls with Turner’s syndrome, because the clinical trials of GH prepared by each pharmaceutical company started independently. After 3 years of each individual clinical trial, the overall trial was transferred to the surveillance of the Foundation of Growth Science in Japan until the preparation became commercially available. In 1991, the Japanese Ministry of Health and Welfare approved GH treatment only for those patients with Turner’s syndrome who had GH deficiency, not on the basis of scientific observation, but from political and economic points of view. As a result, some of the patients who fulfilled the criteria were given commercially available GH preparations and were dropped from our clinical trials. During the clinical trials, adverse events of Creutzfeld-Jakob disease and leukaemia associated with hGH treatment were announced by the mass media. After specialist surveys, it was reported that there was no evidence that hGH treatment increased the incidence of leukaemia. However, these problems may partly explain why about 50% of the patients withdrew from our clinical trial within 3 years. To date, 260 patients (72%) have stopped the clinical trials. Thirty-two percent of them achieved heights within the normal range (current height $\pm 2$ S.D.), but 27% did not attain heights within the normal range and their growth rate was poor. Forty-two percent of the patients withdrew from the clinical trials in spite of heights below the normal range (current height $\pm 2$ S.D.); however, as they were still growing well with hGH, some of them might have continued
The main aim of treatment with GH is to improve the final adult height. To assess the effect of GH treatment, an observation period of more than 6 years was needed. In our series of clinical trials, 115 patients were treated for more than 6 years and 30 patients attained near final height (growth rate ≤ 1 cm/year). We have reported here the effect of two doses of GH treatment. Growth acceleration was observed with both doses; the effect was greatest during the first year and decreased gradually with duration of treatment. These results were similar to those of other studies (16–21). Decreased effectiveness of GH treatment with increased duration of treatment might be due to resistance of the tissue for GH, IGF-I, or both. However, the mechanism of this phenomenon is not clear at present and requires further study. Of the two doses, the larger increased growth rate to a significantly greater degree only during the initial 2 years of treatment. The current height of the patients showed a large variation in each group of patients and the mean final height did not differ statistically between the two dose groups. However, this result does not imply that a higher dose of hGH is not beneficial. One could use a high dose during the initial 2 or 3 years to let the patients reach the height appropriate to induce puberty at an age similar to that in normal girls. Further observations are required to resolve this question. We analysed the factors which influenced final height and found that the height at the start of treatment was correlated weakly to the effect of GH treatment. However, as the number of patients was small, a further study is required to analyse these factors. No serious adverse events occurred during long-term treatment. Glucose intolerance was not observed in any patient and none had antibody to hGH after 6 years of treatment. Without GH treatment, the mean final height of Japanese girls with Turner’s syndrome is 138 cm; the final height was improved by 4–6 cm with GH treatment. These results are similar to those reported by others (22–27).

Recently, the final height of patients with Turner’s syndrome treated with GH has been reported in the USA and Europe (22–27). The design of the clinical study, the age at the start of GH treatment, the period of GH treatment and the definition of the final height were different in each clinical trial. Some papers reported combination therapy with oxandrolone, oestrogen, or both. Massa et al. (21) studied the influence of induced puberty on the growth-promoting effect of GH and found that ethinyl oestradiol 100 ng/kg per day decelerated the growth rate. In our study, 21 of 115 patients were treated with oestrogen. Most of them were treated to induce puberty after the age of 13 years. During the 6 years of treatment, there were no differences in height increase (SDS) among the three groups of patients with different pubertal status; furthermore, the final height of patients treated with oestrogen did not differ from that of others. Nilsson et al. (27) reported that the mean net gain of patients treated with combination therapy with oestrogen was 3–4 cm below the projected adult height, but that combined therapy with oxandrolone significantly improved the final height. The patients treated with GH plus oxandrolone had a mean net gain of 8.5 cm over the projected adult height. These results were similar to those reported by Rosenfeld et al. (22).

From our observations, we conclude that GH therapy in patients with Turner’s syndrome is capable of both accelerating growth and increasing adult height. However, further study is required to enable improved final height and quality of life. By identifying, for example, the ideal age for initiation of GH therapy, the effective dosage and frequency of GH administration, the ideal age for the initiation of anabolic steroid and the effective dosage, and the optimal time and manner of sex steroid replacement therapy.

Table 3 Final height of patients with Turner’s syndrome treated with hGH, from recent reports.

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>GR (mm/year)</th>
<th>FH (cm)</th>
<th>PAH (cm)</th>
<th>Duration of treatment (years)</th>
<th>FH–PAH (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22. Rosenfeld R G et al.</td>
<td>42</td>
<td>≤ 10</td>
<td>151.7 ± 5.6</td>
<td>142.8 ± 6.1</td>
<td>5.2</td>
<td>8.9 ± 5.0</td>
</tr>
<tr>
<td>(USA trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. Van den Broeck J et al.</td>
<td>56</td>
<td>&lt; 4</td>
<td>150.7 ± 4.9</td>
<td>147.8</td>
<td>5–6</td>
<td>2.9 ± 3.8</td>
</tr>
<tr>
<td>(five European trials)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. Attanasio A et al.</td>
<td>6</td>
<td>&lt; 4</td>
<td>150.9 ± 4.7</td>
<td>151.1 ± 6.2</td>
<td>4.4</td>
<td>−0.2</td>
</tr>
<tr>
<td>(German trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. Massa G et al.</td>
<td>45</td>
<td>&lt; 5</td>
<td>152.3 ± 5.3</td>
<td>149.7 ± 5.7</td>
<td>~ 6</td>
<td>2.6 ± 3.5</td>
</tr>
<tr>
<td>(Dutch trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26. Rochiccioli P et al.</td>
<td>117</td>
<td>&lt; 10</td>
<td>147.7 ± 5.6</td>
<td>144.9 ± 5.2</td>
<td>4.0</td>
<td>3.0</td>
</tr>
<tr>
<td>(French trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. Nilsson K O et al</td>
<td>44</td>
<td>≤ 10</td>
<td>152.2 ± 5.9</td>
<td>146.4 ± 5.3</td>
<td>4.1</td>
<td>5.8 ± 4.8</td>
</tr>
<tr>
<td>(Swedish trial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n, Number of patients; GR, growth rate; FH: final height; PAH, projected adult height. * Predicted adult height.
Acknowledgements
The authors are very grateful to Sumitomo Pharmaceutical Co., Ltd (Osaka, Japan), Novo Nordisk Pharmaceuticals, Ltd (Tokyo, Japan) and Eli Lilly Japan K K (Kobe, Japan) for supplying the recombinant human growth hormone used in this study. We also thank Novo Nordisk Pharmaceuticals, Ltd (Tokyo, Japan) for helping with statistical analyses. The authors wish to thank all the participating investigators of these studies.

References