Growth Hormone (GH) Treatment in Turner Syndrome (TS) and Predictors of Response: a Comparison between Japan, Sweden, and the UK as Documented in the Kabi Pharmacia International Growth Study (KIGS) Database

David Anthony Price on behalf of the International Board of the Kabi Pharmacia International Growth Study

Department of Child Health, Royal Manchester Children’s Hospital, Manchester, UK

Abstract. Baseline auxology and responses to growth hormone (GH) treatment in girls with Turner syndrome (TS) from three countries, Japan, Sweden and the United Kingdom, were compared, using data from the Kabi Pharmacia International Growth Study (KIGS). Differences were observed between countries in respect to pretreatment height and height velocity, chronological and bone ages at onset of GH, parental and target heights, body proportions, weight-for-height index, birth weight, and peak GH levels in provocation tests.

Median values for height velocity in the first 3 year of GH treatment were greatest in Sweden and lowest in Japan. A previously derived model for predicting first year response in TS was applied to data from the 3 countries: there was no difference between the Studentised residuals of observed-predicted height velocities between countries.

It was concluded that although there were differences in response to GH between countries, there was no difference in “responsiveness”. The predictive model for first year response was robust but only accounted for 25% of the variability of response; other factors predicting response to GH in TS should be sought.

Key words: Turner syndrome, growth hormone treatment

Introduction

The Kabi Pharmacia International Growth Study (KIGS) contains safety and efficacy data in relation to recombinant GH treatment from many countries and from children of differing racial groups. Recently simple models for prediction of first year response to GH in growth hormone deficiency and other forms of short stature, including TS, have been derived from the database of KIGS (1). A comparison of girls with TS within KIGS from 3 different countries has been made with respect to baseline auxology, growth response and behavior in the predictive model for TS.

Patients and Methods

Girls were selected for comparison if entered into KIGS categorized by their referring physicians as having TS and having started treatment with Genotropin, from 3 countries,
Japan (n=53), Sweden (n=138) and the UK (n=226).

Birth weight and length standard deviation score (SDS) were calculated using the standards of Walli et al. (2). Annual height velocities were calculated if height measurements were available for a minimum of 9 months and a maximum of 15 months apart. Standard deviation scores for height and height velocities were calculated from Tanner standards (3) and from Turner specific standards of Ranke (4). Target height (TH) was calculated for males and females using the equation devised by Tanner (5): TH (cm) = (father’s height + mother’s height ± 13 cm)/2. Sitting height and leg length SDS were calculated using Tanner standards (6). Weight-for-height index was calculated expressing weight as a percentage of ideal weight for height in the normal population. Bone ages were standardized using the regression equation: bone age = 1.61 × (chronological age) - 0.04 (chronological age)² - 3.61 and a SD of 1.3 (7).

Peak GH levels were the highest values recorded from all tests (excluding GRF stimulation) recorded in the Case Record Forms and converted where necessary to mU/L.

The model described by Ranke et al. (1) for predicting first year response to GH was used:

\[
\text{height velocity (cm/year) = } 2.02 - 0.19 \times \text{(age at start of GH)} + 0.28 \times \text{(number of injections/week)} + 1.92 \times \text{(dose of GH IU/kg/week)} + 0.37 \times \text{(target height SDS - height SDS)} + 0.028 \times \text{(weight-for-height index)}
\]

(n = 202; R² = 0.25; error SD = 1.52)

Wilcoxon rank tests were used for comparisons. Median values, 10th-90th centile ranges, and Spearman correlation coefficients and Kruskal-Wallis tests are quoted, and P values correspond to two-sided tests.

**Results**

**Auxology and other parameters before start of GH treatment (Table 1)**

1. Birth weight SDS and birth length SDS. Swedish girls had significantly greater birth weight SDS than UK girls (P=0.002) and Japanese girls (P=0.001). Birth length SDS did not differ between countries, although the number of observations from UK and Japan were much reduced compared with Sweden.

**Table 1** Comparison of auxological and other criteria before onset of GH treatment (median values only)

<table>
<thead>
<tr>
<th></th>
<th>Sweden median (n)</th>
<th>UK median (n)</th>
<th>Japan median (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight SDS</td>
<td>-0.8 (132)</td>
<td>-1.3 (207)</td>
<td>-1.6 (53)</td>
</tr>
<tr>
<td>Birth length SDS</td>
<td>-1.1 (131)</td>
<td>-1.4 (211)</td>
<td>-0.8 (29)</td>
</tr>
<tr>
<td>Paternal ht SDS</td>
<td>0.5 (130)</td>
<td>0.1 (213)</td>
<td>-1.4 (53)</td>
</tr>
<tr>
<td>Maternal ht SDS</td>
<td>0.6 (132)</td>
<td>-0.4 (218)</td>
<td>-1.4 (53)</td>
</tr>
<tr>
<td>Target ht SDS</td>
<td>0.6 (130)</td>
<td>-0.1 (213)</td>
<td>-1.4 (53)</td>
</tr>
<tr>
<td>CA (years)</td>
<td>10.4 (138)</td>
<td>10.5 (226)</td>
<td>12.0 (53)</td>
</tr>
<tr>
<td>BA (Greulich and Pyle) (years)</td>
<td>10.0 (98)</td>
<td>9.7 (122)</td>
<td>9.3 (26)</td>
</tr>
<tr>
<td>BA SDS</td>
<td>0.5 (98)</td>
<td>0.6 (1.1)</td>
<td>0.2 (26)</td>
</tr>
<tr>
<td>Ht SDS (Tanner)</td>
<td>-2.5 (136)</td>
<td>-2.9 (223)</td>
<td>-3.5 (48)</td>
</tr>
<tr>
<td>Ht SDS for TH</td>
<td>-3.0 (129)</td>
<td>-2.7 (210)</td>
<td>-2.2 (48)</td>
</tr>
<tr>
<td>Ht SDS (Ranke)</td>
<td>0.3 (138)</td>
<td>-0.3 (223)</td>
<td>-0.8 (53)</td>
</tr>
<tr>
<td>Weight-for-height %</td>
<td>107.6 (137)</td>
<td>109.0 (218)</td>
<td>118.4 (53)</td>
</tr>
<tr>
<td>Body mass index %</td>
<td>17.7 (137)</td>
<td>17.5 (218)</td>
<td>19.4 (53)</td>
</tr>
<tr>
<td>Siming ht SDS</td>
<td>-2.0 (107)</td>
<td>-2.1 (73)</td>
<td>——</td>
</tr>
<tr>
<td>Leg length SDS</td>
<td>-2.3 (107)</td>
<td>-3.1 (75)</td>
<td>——</td>
</tr>
<tr>
<td>Height velocity (cm)</td>
<td>4.3 (89)</td>
<td>4.6 (100)</td>
<td>3.1 (35)</td>
</tr>
<tr>
<td>Height velocity SDS (Ranke)</td>
<td>0.1 (87)</td>
<td>0.3 (97)</td>
<td>-0.5 (33)</td>
</tr>
<tr>
<td>Peak GH in tests (mU/L)</td>
<td>13.9 (82)</td>
<td>22.8 (182)</td>
<td>17.0 (53)</td>
</tr>
</tbody>
</table>
Predictors of Response to GH in Turner’s

2. Parental and target height SDS. There were significant differences for mother’s, father’s and target height SDS between all 3 countries (P=0.0001) with Swedish parents tallest and Japanese parents shortest.

3. Chronological age (CA). Japanese girls began GH treatment at an age significantly greater than Swedish (P=0.0075) and UK girls (P=0.0006).

4. Bone age (BA) and BA SDS. There was no significant difference in BA between countries but BA SDS was lower in Japan than in Sweden and in the UK (P=0.013).

5. Height SDS, height SDS corrected for TH SDS, and height SDS (Ranke). Height SDS using Tanner or Ranke standards was different between the 3 countries (P=0.0001) with Swedish girls tallest and Japanese girls shortest. When height SDS was corrected for TH SDS Japanese girls had significantly greater values than Swedish and UK girls (P=0.0001).

6. Weight-for-height index and Body Mass Index (BMI). Both weight-for-height index and BMI were greater in Japanese girls than in Swedish (P=0.0014 and 0.0054) and UK (P=0.0016 and 0.0022) girls.

7. Sitting height SDS and leg length SDS. There was no difference in sitting height SDS between Swedish and UK girls but leg length was greater in the former (P=0.0001). (There were no values available for comparison from Japanese girls.)

8. Pretreatment height velocity SDS (Ranke). Japanese girls grew more slowly than Swedish (P=0.02) and UK (0.0006) girls.

9. Peak GH levels in provocation tests. Peak levels of GH in provocation tests were higher in UK girls than in Swedish (0.0002) and Japanese (0.013) girls.

Doses and regimens of GH

The median starting dose of GH was 0.7 U/kg/week in both Sweden and the UK (Fig. 1) and 0.5 U/kg/week in Japan, significantly lower (P=0.0001). The current median dose was 0.7 U/kg/week in Sweden and the UK and 0.4 U/kg/week in Japan (P=0.0001). The variability of dosage was greatest in the UK (Fig. 1). Median weekly frequencies of injections were 7, 6 and 4 at onset of treatment and currently 7, 7 and 6 in Sweden, UK, and Japan respectively.

Response to GH treatment

1. Height SDS (Ranke) (Fig. 2). Height SDS (Ranke) rose in Swedish girls from a median of 0.3 to 1.9 after the 4th year of GH, in UK girls from -0.3 to 1.1 after the 4th year of

Fig. 1 Dose of GH at start of treatment according to country (boxplot 25-75 %, whiskers 10-90 %, bar median value, star mean value).
GH, and in Japanese girls from -0.8 to 0 after the 3rd year of GH.

2. Height velocity. Median height velocity after the first year of GH was 8.8, 6.6 and 5.2 cm/year in Swedish, UK and Japanese girls respectively. Height velocity had fallen to pretreatment levels after 4 years of GH in Swedish and UK girls, but was still above pretreatment levels in Japanese girls after 3 years (the number of Japanese girls was too small after 4 years for comment).

3. Height velocity SDS (Ranke) (Fig. 3). Median height velocity SDS (Ranke) rose from 0.1 to 4.0 after the first year of GH and was still 1.1 after 4 years in Swedish girls. Median height velocity SDS (Ranke) rose from 0.3 to 2.9 after the first year of GH and was still 1.5 after 4 years in UK girls. Median height velocity SDS (Ranke) rose from -0.5 to 2.0 after the first year of GH and was still 2.6 after 3 years in Japanese girls.

4. Observed versus predicted height velocity in the first year of GH treatment. When the studentised residual of observed minus predicted height velocity in the first year of GH treatment was calculated the total population of TS girls from the 3 countries were not statistically different from zero. Dividing the TS girls according to country did not demonstrate any difference (Fig. 4). The first year response of girls from each country therefore fitted the predictive model (see methods). Values for observed minus predicted height velocity for TS girls from each of the 3 countries were not statistically different (Fig. 5).

**Fig. 2** Response to GH treatment expressed as Height SDS (Ranke) according to country: A. Sweden B. UK C. Japan.

**Fig. 3** Response to GH treatment expressed as Height Velocity SDS (Ranke) according to country: A. Sweden B. UK C. Japan.
Predictors of Response to GH in Turner's

Discussion

Common standards were used to compare girls with TS from 3 countries, Japan, the UK and Sweden, in which there are very different values for mean adult female heights, namely 157.7 cm, 161.7 cm and 165.0 cm respectively (8-10). Not surprisingly there were marked differences in parental heights, birth weight and pretreatment heights and height velocities. Differences in clinical practice were also observed with lower and less frequent doses of GH administered in Japan, a wider variation of dose given in the UK (Fig. 1), and later onset of treatment in Japan.

Response to GH treatment differed accordingly with higher levels of height SDS and height velocity seen in Swedish girls and lower levels in Japanese girls. However when response was expressed in height velocity SDS, although the first year values showed the same pattern between countries, by the third year there was no statistical difference between countries.

Ranke et al. (1) developed simple mathematical models by multiple linear regression for the prediction of first year growth in IGHD and other short stature syndromes. They were able to demonstrate that 56% of the variability of first year height velocity in prepubertal IGHD children could be predicted (Table 2). The difference between target height SDS and height SDS at start of GH was the most important predictor accounting for 22% of the variability of response, whereas dose of GH accounted for only 5%. On the other hand the model developed for TS indicated that dose of

Fig. 4 Observed minus predicted height velocity (expressed as a Studentised residual) in the first year of GH in prepubertal girls with TS against predicted height velocity, according to country (mean and ± 2 SDs for model drawn).

Fig. 5 Observed minus predicted height velocities (cm/year) in the first year of GH treatment in prepubertal girls with TS according to country.
GH was the most important predictor accounting for 11% of the first year velocity on GH (the order of importance of relevant predictors is shown in Table 2). This would seem to indicate that TS girls exhibit an entirely different type of response to GH treatment than the catch-up growth seen in IGHD.

Only 25% of the variability of response can be predicted in TS, perhaps surprising in a condition in which growth is so well channeled. Other potential predictors such as the leg length to sitting height ratio and degree of dysmorphism require testing.

When prepubertal girls with TS from the three countries were compared using the predictive model for first year velocity on GH (Figs. 3 and 4) there were no differences observed, either between countries or in comparison with the model. The robustness of the model shown between countries indicates that it may be useful both before GH treatment begins in counseling parent and child as to what growth might be expected and also after the first year of treatment in evaluating possible adverse factors such as noncompliance.

Acknowledgments

I would like to thank Ann-Christin Svensson, Annika Wallström, and others in the KIGS team of Pharmacia in Stockholm, for their assistance and support.

References


Table 2 Models for predicting first year height velocity in response to GH in prepubertal children with IGHD or TS: comparison of ranking of predictors [after Ranke et al. (1)]

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Rank or order of importance in IGHD</th>
<th>Rank or order of importance in Turner's Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target height SDS - height SDS at start of GH</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Frequency of GH injections</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Age at start of GH</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Weight for height index at start of GH</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Starting dose of GH</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Birth weight SDS</td>
<td>6</td>
<td>-</td>
</tr>
</tbody>
</table>
Predictors of Response to GH in Turner's


