Prediction of Long-Term Response to Recombinant Human Growth Hormone in Turner Syndrome: Development and Validation of Mathematical Models

MICHAEL B. RANKE, ANDERS LINDBERG, PIERRE CHATELAIN, PATRICK WILTON, WAYNE CUTFIELD, KERSTIN ALBERTSSON-WIKLAND, AND DAVID A. PRICE ON BEHALF OF THE KIGS INTERNATIONAL BOARD

ABSTRACT
It has become common practice to apply GH treatment in short Turner syndrome patients with the objective of promoting growth. The variability in response and the high costs of this treatment demand the individualization and optimization of therapy. Based on 686 prepubertal Turner patients from the Kabi International Growth Study (KIGS; Pharmacia & Upjohn, Inc. International Growth Database), we undertook a multiple regression analysis of height velocity (centimeters per yr) by using various parameters of potential relevance. Derived prediction models for the first 4 yr of GH treatment were validated with 76 additional KIGS patients and 81 patients from Tuebingen, Germany. Among the 6 predictors identified, the most influential variable for first year growth response was the natural log (ln) of the weekly GH dose. The first year growth response was also correlated with age and distance between height and target height (SD score; both negative) and body weight SD, number of GH injections per week, and oxandrolone treatment given additionally (positive). The first year model explains 46% of the variability, with 1 SD of 1.26 cm. For the second to fourth years, 5 predictors were identified: height velocity during previous years, weekly GH dose (ln), weight SD, oxandrolone therapy (all positive), and age (negative). These models explained 32%, 29%, and 30% of the variability, respectively, with SD scores of 1.1, 1.0, and 1.0 cm, respectively. When the models were applied to the other cohorts, no significant difference was noted between observed and predicted responses. Although the parameters used in our models do not entirely explain the variability in the growth response in Turner syndrome, the parameters themselves were clinically relevant to our present understanding and proved to be of high precision. Some of the tested markers, such as karyotype, do not contribute to the growth response. These variables make the models practical and suitable for planning beneficial and cost-effective therapy. (J Clin Endocrinol Metab 85: 4212–4218, 2000)
Patients

By February 19, 1999, there were 3301 TS patients enrolled in KIGS. The database included 762 girls who had received at least 2 yr of GH treatment and for whom we had complete data, of whom 686 were used for developing the prediction models, and 76 (10%) were randomly selected from a dataset sorted according to country and hospital and were reserved for the validation. The diagnosis was made by the treating physician, according to the KIGS Etiology Classification List (code 3.2.1.) and through karyotype tests based on peripheral leukocytes. In 70% of all patients, the findings revealed the 45,X karyotype. Height measurements were recorded at intervals of 9–15 months to determine annual height velocity. Patients who missed GH injections for more than 14 days during the first year were not included in the analysis (they accounted for 3% of the total cohort).

Complete longitudinal data for the first 2 yr of GH treatment were available in 681 prepubertal cases, and in 294 of these patients data collection extended over 4 yr and could thus be used for an analysis of the third and fourth years of treatment.

Statistical analysis

Growth responses (height velocities, centimeters per yr) were correlated with several patient variables by means of multiple regression analysis. These variables are reported as the median and range as well as the mean ± sd. sd scores were calculated as follows: sd score = (patient value − the mean value for age of normal TS) / sd of the value for age- and sex-matched normal subjects or references for TS patients.

Height was analyzed by applying Tanner’s height standards for normal children (9, 10) and Ranke’s Turner-specific standards (11). Calculations of weight and body mass index were based on the British reference data reported by Freeman et al. (12). Birth weight and birth length for gestational age were transformed to sd values using the standards of Niklasson et al. (13). The midparental height (MPH) sd score was calculated according to the method of Ranke (2). Bone ages, based on the method of Greulich and Pyle (14), were taken as reported by the treating physicians.

The following variables were studied: 1) status at birth: weight sd score, length sd score, and ponderal index; 2) genetic background: mother’s height sd score, father’s height sd score, MPH sd score, karyotype (45,X vs. other karyotypes), and ethnic origin (Asian vs. non-Asian); 3) treatment modalities: GH dose [international units per kg BW and per kg ideal BW (weight for height)], frequency of GH injections per week, and additional oxandrolone therapy.

The prediction models were developed by means of multiple linear regression analysis fitted by least squares and the REG procedure in the SAS computer program (version 6.12, SAS Institute, Inc., Cary, NC). A hierarchy of predictive factors was derived by the all possible regression approach, using Mallows’s C(p) criterion for ordering predictive factors, as described by Weisberg (15). Differences between observed and predicted height velocities were expressed in terms of Studentized residuals.

Model validation

For the validation of the prediction models, data from 2 cohorts of patients were used: 1) a cohort of 76 patients with TS enrolled in KIGS, who fulfilled all of the inclusion criteria for a model analysis but were randomly assigned for validation and not for model development; all of these patients were treated with Genotropin; and 2) a cohort of 81 patients diagnosed and treated at the Children’s Hospital (Tuebingen, Germany). The patients were treated with a variety of commercially available recombinant GH products. Data were available for 74, 56, 42, and 30 patients for the first, second, third, and fourth years, respectively.

Results

Demographic characteristics of the cohorts

The characteristics at the start of GH treatment of the Turner patients enrolled in KIGS are listed in Table 1a. Equiv-

alent characteristics, apart from age, of the patients whose data were used for the derivation of the prediction models and who were treated consecutively for 2 and 4 yr are listed in Tables 1b and c, and Fig. 1, a and b.

In the total KIGS cohort, the spontaneous onset of puberty (B2) was observed in 298 patients at a mean age of 13.0 yr, but never before 10 yr. Estrogen substitution (n = 1205) was introduced at a mean age of 14.0 yr, but not earlier than 11 yr.

Growth predictors and growth prediction models

The variables found to be predictive of height velocity in the first 4 yr of treatment, their rank order as predictors, the overall correlation coefficients of the prediction models, and the error sd of their predictions are listed in Table 2. All single predictors were significant at a level of P < 0.001. The equation describing the predicted height velocity (PHV) for the first year of GH therapy is as follows: predicted height velocity (cm/yr) = 8.1 + [2.2 × GH dose (ln; IU/kg × week)] + [−0.3× age at onset (yr)] + [0.4 × body weight sd score] + [−0.2 × (height sd score − MPH sd score)] + [0.4 × number of injections per week] + [1.6 × (oxandrolone = 1; no oxandrolone = 0)] [±1.26] (refer to Table 2).

This model explains 46% of the variability of the response. The parameter of the natural log (ln) of the weekly GH dose was the most important predictor of the six identified. In addition, the growth response was negatively correlated with chronological age and the distance between the children’s present height sd score and the MPH sd score. Therefore, the younger and smaller the child, the greater her first year response to GH therapy. The first year growth response was positively correlated with body weight sd score, frequency of GH injections per week, and additional oxandrolone therapy.

Five variables were found to be important for predicting second, third, and fourth year responses: height velocity during the previous year, body weight sd score, chronological age, weekly GH dose (ln), and oxandrolone therapy. These models for the second, third, and fourth years explain 32%, 29%, and 30% of the variability in response, respectively, with error sd of 1.09, 0.99, and 1.01 cm, respectively (see Table 2). Height velocity during the previous year was the most important and consistent predictor.

Validation of prediction models

The plots of the Studentized residuals (see Subjects and Methods) vs. predicted response in the original KIGS cohorts, based on the four models for the first to fourth year growth responses, are illustrated in Fig. 2, a–d. Studentized residual plots are used to identify outliers, nonlinearity, and nonconstant error variants in prediction models and are part of their mathematical validation. The fact that the observations are randomly clustered implies that there is no heterogeneity in the groups with respect to the relevant importance of the different predictors. Table 3 shows the Studentized residuals for the predicted response during each year, calculated for each of the cohorts studied prospectively for validation. The growth response in the validation groups was not signifi-
The characteristics of the KIGS cohort used to validate the models were similar to those of the cohorts from which the models were derived, except for age (Table 3). There were no statistically significant differences between the predicted and observed responses for each of the 4 yr.

**Discussion**

Treatment with GH for the improvement of growth in TS patients became standard clinical practice after it was reported by Rosenfeld et al. (16) and others (6, 17) that the administration of GH can improve adult height. Neverthe-
less, although the indication is approved in many countries, discussion about this treatment continues. One of the main objections raised is that the results were mainly based on open, uncontrolled observations rather than on randomized, controlled studies. It has also been argued that the selection of patients is biased in these reports, and that it is incorrect to use historical controls to evaluate the effect of treatment (18). These arguments cannot be completely refuted. Nevertheless, the data from a survey such as KIGS allow the analysis of observations from very large cohorts treated within the wide spectrum of medical practice, rather than of data collection limited by the study design (e.g. inclusion criteria, treatment modalities, exclusively large centers, contingent number of patients, costs, the ethical concerns of placebo treatment, etc.). This is why we believe that prediction models developed from patient groups such as those from KIGS, as evidence-based medicine reflecting physicians’ practice, are suited to further improving our understanding of the effects of GH. As shown in Table 1, a–c, the TS patients enlisted in KIGS show essentially the same characteristics as those of large cohorts (19–21). Thus, there is no indication of a selection bias.

The average dose of GH given in TS patients is about 1.5 times the replacement dose for GH deficiency. The oxandrolone dose given to the TS patients is analogous to that commonly used in clinical trials (4), and it is assumed that it is low enough to avoid causing virilization (median, 0.05; range, 0.03–0.10 mg/kg per day).

The general aims in treating growth failure in children with TS are principally the same as those in children with GH deficiency. Firstly, the children are treated so as to grow as normally as possible. This means that their height deficit

---

**TABLE 2.** Regression equation for predicting height velocity (centimeters per yr)

<table>
<thead>
<tr>
<th></th>
<th>First yr (n = 686)</th>
<th>Second yr (n = 681)</th>
<th>Third yr (n = 293)</th>
<th>Fourth yr (n = 291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter estimate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept (constant)</td>
<td>8.1</td>
<td>6.0</td>
<td>5.6</td>
<td>4.8</td>
</tr>
<tr>
<td>GH dose (ln IU/kg-week)</td>
<td>2.2</td>
<td>1.1</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Age at onset (yr)</td>
<td>-0.3</td>
<td>-0.1</td>
<td>-0.1</td>
<td>-0.1</td>
</tr>
<tr>
<td>Weight (SD score)</td>
<td>0.4</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Oxandrolone therapy</td>
<td>1.6</td>
<td>1.0</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Ht – MPH (SD score)</td>
<td>-0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>No. of injections/wk (6 or 7)</td>
<td>0.4</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Ht velocity/previous yr (cm/yr)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>( r^2 )</td>
<td>0.46</td>
<td>0.32</td>
<td>0.29</td>
<td>0.30</td>
</tr>
<tr>
<td>Error SD (cm)</td>
<td>1.26</td>
<td>1.09</td>
<td>0.99</td>
<td>1.01</td>
</tr>
</tbody>
</table>

**FIG. 1.** Height of patients with TS at the start of GH therapy compared with normative (shaded area) and TS references (12) (±2 SD). a, Patients (n = 686) treated longitudinally for 2 yr; b, patients (n = 294) treated longitudinally for 4 yr.
should be reduced, and growth should be close to the age-related norms for girls. The patients should then continue to grow within the normal range, which would mean that puberty can be medically induced in a timely manner, and, ultimately, they should reach a normal adult height. Secondly, any possible risk posed by GH therapy should be minimized. Thirdly, to limit costs, the normalization of height should be attained by means of the lowest possible cumulative dose of GH.

In contrast, it is a difficult task to define the appropriate level of growth required, in numerical terms, to reach all of these goals. The response to GH treatment is a function of treatment modalities, such as the dose of GH, the frequency of injections, any concurrent treatment affecting growth such
as oxandrolone or estrogens, as well as the individual response to such preparations. The responsiveness may be determined by age, body composition, and GH secretory status.

In recent times, multiple regression analyses have been made of the factors determining the growth response to exogenous GH in patients with GHD, which were based on large cohorts participating in multicenter studies (22–24). Subsequently, mathematical models to predict the response to GH in prepubertal (8) and pubertal (25) children with GHD have been derived and validated. Similarly, in patients with TS, the factors determining the first year growth response (20) and the overall response from the start of treatment to adult height have been analyzed (26).

In a previous KIGS study, a cohort of 202 patients with TS was analyzed (20). The present analysis of KIGS data is based on larger cohorts, which were observed longitudinally. It was restricted to patients receiving 6 or 7 injections of recombinant GH/week. The present first year model, based on 686 patients, explained 46% of the variability of the response with an error sd of 1.26 cm, and GH dose (ln) proved to be the most important predictor. Age (negative), weight sd score (positive), distance of height sd score to MPH sd score (negative), concurrent therapy with oxandrolone or its absence, and the frequency of injections (positive) were further predictors of the first year’s response to GH (Table 3). Interestingly, however, the karyotype did not show predictive value. The relationship between the genetic constitution and short stature as well as GH responsiveness may need further study in the future.

Height velocities during the second, third, and fourth years of GH treatment were predicted by the same five variables. These were height velocity during the previous year, GH dose (ln), age (negative), weight sd score, and the introduction of oxandrolone. The height velocity of the previous year was the most important predictor, a fact indicating that the height outcome of a patient may be indicated by her initial response to GH. The accuracy of the predictions in all 4 yr, as evidenced by the low error sds, was high. However, as in patients with GHD, the predictive power ($r^2$) during the second to fourth years is relatively low, with slight variation.

The model might therefore have to be expanded to include additional parameters that have yet to be identified in seeking an explanation for the variability in response. The advantage of the present model is that it is based on robust and easily accessible parameters.

It must also be noted that the positive effect of oxandrolone during the first 4 yr is by no means an assurance that concomitant treatment will improve adult height, as the implications of such a premise would inevitably be a reduction in the total GH dose.

In the present study the prediction model was validated on the basis of a cohort taken from KIGS data and another cohort from a single center (Tuebingen). These patients reflect the wide variation between TS patients at the onset of GH therapy, and in the case of the Tuebingen cohort, the different brands of recombinant GH that may be applied. There was no statistical difference between the observed and predicted height velocities either in the different groups or in years, and our findings showed the same range of Studentized residuals as for the groups used for derivation of the model. This observation confirms the usefulness of the prediction equation and suggests that the different recombinant human GH products are equivalent to each other in efficacy.

Such models may aid clinicians in several ways. For example, prediction models could be used to calculate expected height velocities at the start of GH treatment on the basis of the characteristics of the patients and putative treatment modalities. Differences between the observed and predicted height velocities will become apparent and potential explanations will be sought. Prediction models could also be useful during the planning stage of individual treatment regimens. By using the models to hypothetically vary the amount of GH to be given per yr, an estimate of the response in relation to costs can be made. These models may also help to provide the patients, their parents, treating physicians, and health providers with realistic expectations of the short-term (yearly) and long-term growth outcomes of treatment. A rationale for considering continuation or discontinuation of treatment would thus also be provided.

The authors hope that the model presented here will be of practical benefit in guiding treatment and that it will serve as a foundation in the future, once further anthropometrical, functional, and biochemical data become available.

Acknowledgments

We thank the physicians who contributed Turner patient data to KIGS. We are also grateful to Priscilla Herrmann for her assistance in preparing this manuscript.
References