Personalized Approach to Growth Hormone Treatment: Clinical Use of Growth Prediction Models

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Key Words

Growth hormone deficiency · Idiopathic short stature · Small for gestational age · Insulin-like growth factor I · Growth hormone receptor

Abstract

The goal of growth hormone (GH) treatment in a short child is to attain a fast catch-up growth toward the target height (TH) standard deviation score (SDS), followed by a maintenance phase, a proper pubertal height gain, and an adult height close to TH. The short-term response variable of GH treatment, first-year height velocity (HV) (cm/year or change

in height SDS), can either be compared with GH response charts for diagnosis, age and gender, or with predicted HV based on prediction models. Three types of prediction models have been described: the Kabi International Growth Hormone Study models, the Gothenburg models and the Cologne model. With these models, 50–80% of the variance could be explained. When used prospectively, individualized dosing reduces the variation in growth response in comparison with a fixed dose per body weight. Insulin-like growth factor-I-based dose titration also led to a decrease in the variation. It is uncertain whether adding biochemical, genetic or proteomic markers may improve the accuracy of the prediction. Prediction models may lead to a more evidence-based approach to determine the GH dose regimen and may reduce the drug costs for GH treatment. There is a need for user-friendly software programs to make prediction models easily available in the clinic.

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Introduction

In 1986, biosynthetic growth hormone (GH) became available, which led to a rapid expansion of indications and clinical trials to study the effect of various dose regimens. At present, GH is approved for GH deficiency (GHD) in children and adults, and for the treatment of short stature in a number of diseases not associated with impaired GH secretion. However, the challenge is how to optimize GH treatment with respect to growth, safety and cost [1].

There is a high individual variability in the growth response to GH treatment across all diagnoses, suggesting variable GH sensitivity (responsiveness). A significant proportion of patients do not attain an adult height (AH) within the familial target range, even after many years of treatment [2]. This would imply that instead of a fixed GH dose per body weight (kg) or surface area (m²), the GH dosage could be personalized. This might not only improve the result in terms of growth and safety, but also give a better cost-benefit ratio. The strategies that have been employed in this regard include: (a) *prediction model-based dosing*, based on estimated responsiveness, whereby baseline auxological and biochemical characteristics of patients determine the starting GH dose; (b) *auxology-based dosing*, in which the size-based GH dose is increased if the growth response is lower than expected, and (c) *insulin-like growth factor-based dosing*, an approach that involves GH dose titration designed to achieve a desired IGF-I standard deviation score (SDS) level.

Fig. 1. Concept of GH treatment through a lifespan. With permission from Krström and Albertsson Wikland [25].

In this mini review the possibilities and prospects of a personalized approach to GH treatment are discussed, based on contributions by the authors at a meeting dedicated to this topic (Nice, France, February 2012).

Measures of Success of GH Treatment

Goal and Definition of a Successful GH Treatment, Outcome Measurements and Quality Indicators

The goal of GH treatment in a GHD child is to attain 'true' catch-up growth (CUG) [3]. This consists of a first phase of rapid growth, which takes the height of the child toward the target height (TH) SDS in a number of years (depending on the age and initial height deficit), followed by a phase of maintenance growth where height velocity (HV) is normal. After a normally timed and adequate pubertal growth spurt, AH comes close to TH (fig. 1). Ideally, this should be attained with a normal serum IGF-I concentration, and at the lowest possible cost.

Although such growth response can be observed in many children when treated with GH in a fixed dosage per body size, this approach is associated with two unresolved issues. First, there is no consensus about the appropriate dosage [4, 5], possibly associated with the broad range of GH secretion rate and bioavailability of administered GH [6]. Second, there is a wide interindividual variation of the growth response to any dosage per body size, indicating the broad range of GH responsiveness.

Table 1. Phases of growth in response to GH treatment and relevant outcome measures

Phase	Outcome measures per age at treatment initiation	
	young children	peripubertal children and adolescents
Initial catch-up	parameters of speed and duration (corrected for age, distance to TH and severity of GHD); integrated measure: sufficiency (height SDS – TH SDS after initial phase)	parameters of speed, duration and sufficiency are mixed with pubertal growth spurt; thus difficult to analyze
Maintenance	position (height SDS – TH SDS)	absent
Pubertal growth	pubertal height gain (corrected for gender and age at start of puberty)	mixed with catch-up phase, size difficult to assess; dependent on pubertal timing, puberty induction, GnRHa treatment
Adult height	adult height SDS – TH SDS	adult height SDS – TH SDS

GnRHa = Gonadotropin-releasing hormone analogue.

In theory, the response to GH treatment can be studied over various phases (initial catch-up, maintenance phase, pubertal growth spurt, and AH), using different outcome measures (table 1). However, the response variable that is used most often is the first-year (1st-year) growth response, either expressed as HV (cm/year), change in height SDS, HV SDS adjusted for age and gender, or the change in HV (1st-year HV minus pretreatment HV) [7]. All these measures depend on age and on the initial distance between height SDS and TH SDS (DiffH-THSDS), and none of them incorporate bone maturation. Still, there is a significant positive association between the 1st-year response with long-term outcome [8–10].

AH is not only dependent on the completeness of the initial phase of CUG, but also on the appropriateness of the maintenance phase and pubertal growth. The pubertal height gain can be manipulated, for example by delaying induction of puberty, treatment with gonadotropin-releasing hormone analogues [11, 12], or addition of aromatase inhibitors [13]. There are equivocal results of increasing the GH dose in puberty [14–16].

Quality of the Growth Response Achieved in Various Diagnostic Groups

Several long-term studies on GH treatment were carried out in Sweden. In GHD children, it took an average of 4–5 prepubertal years to reach TH SDS on a dose of 33 µg/kg/day, and the average attained AH was close to TH [4]. In clinical trials on doubling the dose in puberty in adolescents with GHD or non-GHD children (idiopathic short stature (ISS) or born small for gestational age (SGA)), a dose-dependent AH SDS gain was ob-

served [14, 17], but on both regimens AH was close to TH.

In a Spanish cohort of 184 children, part of a larger cohort [18] with idiopathic GHD, ISS or SGA, treatment with GH in an average dosage of 32 µg/kg/day up to AH resulted in a similar AH (0.4–0.5 standard deviation (SD) below TH) and AH gain (1.6–1.7 SD), irrespective of diagnosis [19]. In the Netherlands, France and Japan, where generally lower GH doses have been used, average AH was 1.6–2 SD lower than TH [20–22].

Age- and Gender-Specific Targets for First-Year Growth Response

The databases from National Cooperative Growth Study (NCGS) [23] and Kabi International Growth Hormone Study (KIGS – Pfizer International Growth Database) [24] were employed to construct plots of 1st-year growth response during treatment with ‘standard’ GH doses (close to 43 µg/kg/day in NCGS, and a mean dose of 29 (range 9–61) µg/kg/day in KIGS) in prepubertal children aged 2–14 years at the onset of therapy. Outcome variables included HV, change in height SDS and HV SDS, and GH response curves were generated for each etiology and gender. In general, the mean pretreatment HV curve approximated the 1st-year –2 SDS curve. A 1st-year growth response <–1 SDS was arbitrarily defined as a ‘poor’ response, justifying re-evaluation of the patient. The mean response curve in GHD was ~2 cm/year higher in the NCGS compared to the KIGS data, reflecting a ~50% higher ‘standard’ dose in the USA. For the GHD groups the mean response curves were ~2 cm/year higher than in other diagnoses, while the –1 SDS curves were

Table 2. Goals and requirements for clinically relevant prediction models

Prediction models can be used:
– to identify poor responders (prospectively or retrospectively)
– to determine the GH dose needed to achieve a child's TH SDS as rapidly as possible
– to provide realistic expectations about the growth response
– to foster development of dosing strategies using the lowest possible cumulative GH dose
An ideal prediction model should:
– be validated using an independent cohort of the same group of patients
– have a small prediction error
– explain as much as possible of the variability in treatment response
– be based on readily available and standardized variables
– include treatment modalities as variables
– be based on biological principles
– be easy to use in clinical practice
Adapted from Geffner and Dunger [68] and Ranke et al. [30].

at similar levels for all diagnoses, suggesting that the GHD cut-off for 'poor' response would apply to all diagnoses. For all conditions, mean 1st-year HV varied with age at baseline, but its SD varied minimally with age. In contrast, the mean and SD of change in height SDS and HV SDS varied substantially with age.

Concepts and Examples of Growth Prediction Models

Principles of Prediction Models

Since 1st-year HV is dependent on more factors than age, gender and diagnosis alone, three groups of investigators built growth prediction models. A prediction model predicts future height (gain) based on patients' characteristics and modalities of GH treatment (predictors). The goals and requirements for clinically relevant prediction models are summarized in table 2.

The indicator of how well the model predicts, is the SD of the residuals (SD_{res}), a residual being the difference between the individual observed height and the predicted height. The lower the SD_{res} , the better the prediction (0 is best, scaled in cm or SDS). Another indicator is the amount of variance explained (R^2); the higher the R^2 the better (1 is best, scaled 0–1). The uncertainty of the prediction can be expressed as a 95% prediction interval

Table 3. Comparison of the three models^a described in the respective paragraphs in the text

	KIGS	Gothenburg	Cologne
Use an appropriate design and measurements	yes	yes	yes
Include appropriate predictors (including interactions)	no	yes	no
Use adequate sample size	yes	yes	no
Avoid categorizing continuous data	yes	no	yes
Check modeling assumptions:			
(a) Independency of errors	no	no	no
(b) Normal residuals	no	no	no
(c) Assess nonlinearity	no	yes	no
(d) Homoscedasticity ^b	yes	yes	yes
Deal with missing data	no	no	no
Estimate predictive power in validation sample	yes	yes	yes ^c
Apply efficient model validation techniques	yes	no	no
Statement of predictive accuracy	yes	yes	yes
Limited to baseline predictors	yes	yes	no
Use of early response variables	no	no	yes

^a Three publications were used for this comparison [26–28].

^b Equal variance of residuals over age and other predictors. ^c Validation performed by Land et al. [38].

[25]. Table 3 shows how three prediction models [26–28] comply with several requirements for a good predictive model.

The application of prediction algorithms to patients' data allows for developing realistic ideas about their short- and long-term growth potential. Differences between predicted and observed growth response give reason to search for causes, such as non-adherence, additional diseases such as hypothyroidism, celiac disease, etc., and may have therapeutic consequences, including a modification of the GH dose or even the termination of GH treatment. Interactive observing and analyzing the growth response during treatment make it possible to tailor therapy to the needs of the patients, while also considering costs.

Recent developments in the field of biostatistics are now available to further increase the accuracy of prediction models. For example, it is possible to check several modeling assumptions, and there are several new methodological approaches to overcome previous limitations [29]. However, these may only modestly improve growth prediction [Ranke, unpubl. data].

KIGS System of Growth Prediction

The approach based on data from KIGS (a voluntary pharmaco-epidemiological survey for children treated with Genotropin™) is based on the hypothesis that optimizing and individualizing GH therapy can be essentially supported by comparing the individual growth response to GH therapy with the observed growth response in groups of patients with specific diagnoses. Group data are used to describe (predict) the most likely growth response – annually or over several prepubertal years, during puberty or from start to AH – with the help of patients' characteristics and modalities of GH treatment (predictors). All predictors used can be measured with high accuracy and are available in daily practice. These prediction models attempt to explain as much of the variability of the growth response at the lowest possible margin of error ($R^2 > 40\%$; coefficient of variation error $< 15\%$). Models have been derived from large groups of patients ($n > 300$) with GHD, Turner syndrome (TS), SGA, ISS and chronic renal insufficiency by means of multiple linear regression (all possible regression approach) [30–32], without imputation of missing data. All KIGS models contain GH dose as a predictive variable, are validated and have proven to be robust. By comparing the predicted with the observed response in an individual, a surrogate term for the responsiveness to GH (index of responsiveness (IoR)) can be calculated. The IoR established after the 1st year on GH is highly correlated with the AH and AH gain.

Gothenburg Prediction Models

The Gothenburg prediction model approach [27, 33, 34] was focused on the large group of prepubertal short children in whom it is not easily recognized if they are GHD or not. In these studies not only the GH peak in a provocation test ($GH_{\max}$) was included, but also the maximum peak during a 12- or 24-hour spontaneous GH profile ($GH_{\max 12/24h}$) [33], which often give different results [35, 36]. Independently of the approach, a continuum of GH secretion is found, so that any dividing line between normal and deficient GH secretion is arbitrary. There is also a continuum of GH sensitivity, as illustrated by the broad range in growth response to a given GH dose [37].

Mathematically the responsiveness is equal to the response per dose, however in the first Swedish studies the children ($n > 400$) were treated with the same dose/kg. In a linear multivariate analysis, 33% of the 1st-year growth response was explained by DiffH-THSDS, $GH_{\max}$ and age at GH start [37], the classical variables used for decision on treatment or not. In this study, $GH_{\max}$, $GH_{\max 24h}$, se-

rum IGF-I and insulin-like growth factor binding protein 3 (IGFBP-3), as well as data on early growth were available for many children. The change in height SDS was chosen as response variable. In the model group, $GH_{\max}$, $GH_{\max 12/24h}$ and serum IGF-I and IGFBP-3 were available for many children, as well as data on early growth. Besides variables found previously [37], other statistically significant predictors included size at birth, height deviation until age 2 years ('early growth'), height 1 year before start of GH, and height and weight at start. Inclusion of early growth data decreased the SD_{res} for the 1st year from 0.28 to 0.24 SDS [27, 33, 37]. The best result was obtained when auxology at start, early growth data and $GH_{\max 12/24h}$ were included (SD_{res} 0.19 SDS) [33] (fig. 2). Later, models were developed for idiopathic growth hormone deficiency (IGHD), ISS, SGA and preterm born children [9, 34]. In the absence of pretreatment data, the observed 1st-year response to treatment predicts the following years of prepubertal growth [9].

Cologne Model

This model [28] was developed in a prospective multicenter trial with 1 year of follow-up on 58 prepubertal patients with GHD. Auxological measurements, parameters of GH status and markers of bone metabolism were measured at baseline and at 1, 3 and 6 months on GH treatment. Correlations with 1st-year HV were calculated and prediction models were derived by multiple regression analysis.

The model which best predicted 1st-year HV included pretreatment bone age retardation as a fraction of chronological age, pretreatment serum IGF-I levels, urinary levels of deoxypyridinoline (a marker of bone resorption) at 1 month of treatment and HV at 3 months of treatment. This model explained 89% of the variation in 1st-year HV with an SD_{res} of 0.93 cm/year. Defining successful GH therapy as a doubling of pretreatment HV, the model had a specificity of 90% and a sensitivity of 100% in predicting therapeutic success [28].

A later study was aimed at validating the model in an independent cohort of 210 prepubertal and pubertal patients with isolated GHD [38]. The model fulfilled the statistical prerequisites to identify patients with poor and good responses to GH with sufficient reliability in individual patients. However, it is important to note that this model is different from the other two models in incorporating not only baseline data, but also the early response with respect to growth and a metabolic marker.

Fig. 2. **a** Growth response (change in 1st-year height SDS) versus GH_{max} in an arginine-insulin tolerance test. **b** Illustration of the prediction interval. With permission from Krström and Albertsson Wikland [25].

Experience with Using Growth Prediction Models

Studies have been performed in several countries aimed at investigating whether the published prediction models were applicable locally. In Barcelona (Spain) the growth response of 475 prepubertal children (classified as GHD, ISS or SGA) was compared with the children included in the KIGS database. There was no statistical difference in the anthropometric characteristics at start, GH dose, and the IoR after 1 year versus KIGS patients classified as GHD or ISS. In the subgroup of SGA children with GHD, the IoR was significantly higher than expected for all SGA children [Audi, pers. commun.].

Several studies have been carried out in the Netherlands on response criteria and growth prediction models. As a first response criterion for 1st-year HV for all indications the formula: $11 - (0.5 \times \text{age})$ in cm/year was used, which is close to a HV >2 SDS. In a study on predicting AH SDS in 342 children with GHD with a mean duration of GH treatment of 8 years, significant predictors were TH SDS, height SDS at start, GH_{max}, gender, multiple pituitary hormone deficiency and bone age at start (R^2 0.43,

SD_{res} 0.79) [39]. After 1 year GH treatment the prediction of AH SDS had a higher R^2 (0.51, SD_{res} 0.69). The predictors in the prediction model for AH SDS for short children born SGA children included height SDS start, GH dose $\times$ IGFBP-3 SDS, bone age delay at start (year), TH SDS, IGFBP-3 SDS at start, and GH dose (1 vs. 2 mg/m²/day) [40].

In a retrospective study in the Nordic countries [41] the objectives were to assess the proportion of poor responders to GH treatment during the 1st year of treatment and assess the value of three prediction models [27, 34, 42] in proactively identifying poor responders in children with GHD, ISS and SGA. The 1st-year change in height SDS within all subgroups showed a wide variation (fig. 3). Both the HV (cm/year) and Δ Ht SDS showed a significant negative correlation with age. GHD patients with a GH_{max} >3 μ g/l showed a response comparable to that of ISS; only children with severe GHD had a better response. Patients with IGHD, ISS and SGA had overlapping positions in the continuum of defects in the GH-IGF axis, and the variation of growth responses within each diagnosis was considerably larger than the mean differ-

Fig. 3. Growth response (expressed as the mean change of height SDS $\pm$ 1 SD) of children treated with GH in the Nordic study, plotted on theoretical diagnostic groups. Strictly speaking, the growth response is not identical with 'GH sensitivity', rather the GH response is determined by responsiveness (sensitivity) $\times$ dose. SPIGFD = Severe primary IGF-I deficiency. Adapted from Savage et al. [70], Bang et al. [41] and Bang (pers. commun.).

ences in responses among the diagnoses. Many patients (independent of their diagnosis) treated with GH for 1 year did not show the expected CUG.

Prospective Studies on Personalized GH Regimens

Swedish Prediction-Based GH Dosing Study

In prepubertal short children, naive to GH treatment, the predicted growth response to GH in a dosage of 33 μ g/kg/day was calculated with the prediction model including early growth variables and the GH_{max24h} [27] and used as an estimate of responsiveness. This was then used to determine the GH dosage in order to reach a pre-set height goal (midparental height (MPH) SDS) [36]. 75% of the children were GHD (defined by a low GH response ($<10 \mu$ g/l) during the arginine-insulin tolerance test). One third of the patients were randomized to the control group with weight-based GH dosing (43 μ g/kg/day) and two thirds to the actual study group with GH doses ranging from 17 to 100 μ g/kg/day (individualized adjusted dose, IAD) (fig. 4). The variation in growth response in the IAD group was reduced by 32%. Since a similar mean GH dose was given in the study groups, the study arms showed similar mean DiffH-MPHSDS. Individualized GH dosing also led to reduced variation in fasting insulin and homeostatic model assessment compared to controls [43]. When the children were reclassified according to GH_{max24h} as GHD or non-GHD, in both groups the same mean gain in height SDS was found, however at a higher mean dose in the non-GHD group: 49 μ g/kg/day compared to 40 μ g/kg/day for GHD.

GH Treatment Optimization Based on Early Growth Prediction: Results from the OPTIMA Study

In this study, the possible benefit of an IAD of GH (based on the Cologne early growth prediction (EGP) model) versus a fixed dosage was investigated in short children born SGA [44]. After the initial 3 months the EGP model allows prediction of height gain at 12 months of GH treatment [28]. Short prepubertal children (height ≤ -3 SDS) were randomized to open-label GH at either a fixed high dose (FHD; $n = 89$) or an IAD ($n = 80$). The FHD group received GH at 67 μ g/kg/day throughout. The IAD group received GH at 35 μ g/kg/day for 3 months and then either remained at the same dose if the predicted 1-year height SDS gain was ≥ 0.75 or received an increased dose of 67 μ g/kg/day if the predicted gain was <0.75 . After 3 months, 38 children in the IAD group on the low GH dose had a predicted 1-year height SDS gain <0.75 and were switched to the higher dose, while 42 patients in this group remained on the low dose. After 1 year of GH treatment, mean height SDS gain for the IAD group was significantly lower than for the FHD group. However, the predefined non-inferiority margin of -0.5 SDS in height was met, the lower limit of the 95% confidence interval (95% CI) being well above this threshold (95% CI -0.35 ; -0.12), with a least square mean difference in height SDS (IAD – FHD) of -0.24 . The mean difference in height between both groups after 1 year of GH treatment was 1.0 cm.

Fig. 4. Concept of individualizing GH dosing. With permission from Krström and Albertsson Wikland [25].

ISS Target-Driven Therapy: The Initial 2 Years of the US Trial

In 2007, enrollment began in a 4-year, multicenter, two-arm trial of GH (Genotropin®; Pfizer, Inc., New York, N.Y., USA) in subjects with ISS comparing an IAD aimed at achieving a TH gain within 2 years to traditional weight-based dosing. The initial phase was followed by a decrease to near-physiological dosing for the remaining 2 years in the IAD group compared to traditional weight-based dosing maintained for 4 years. The GH dose was either calculated at baseline (ranging from 18 to 100 µg/kg/day) using an individualized formula or a standard dose of 37 µg/kg/day. The individualized dose was calculated based on parental heights, as well as auxologic criteria from birth, the first 2 years of life, and the year before starting treatment, and was targeted to reaching a height SDS minus TH SDS of -1.3 by year 2 of the trial. Thereafter, subjects on the IAD were re-randomized to a dose of either 18 or 24 µg/kg/day to assess the minimum dose needed to maintain achieved height gain, while the weight-based arm continued at 37 µg/kg/day and growth rates were monitored. The analysis of this trial is ongoing.

Personalized GH Dosing to Accommodate Individual Variability in GH Sensitivity: Utilization of IGF-Based Dose Titration

In the USA, three randomized-controlled studies were carried out to define potential improvements in GH treatment. The first was a 2-year dose-response study in GHD children randomized to 25, 50, and 100 µg/kg/day of GH [45]. The second study was a 2-year IGF-based dose titra-

tion study in which IGF-deficient (IGFD) children (with either GHD or ISS) were randomized to a fixed (40 µg/kg/day) or variable (designed to reach 0 SDS or +2 SDS of IGF-I) doses of GH [46, 47]. Thirdly, a 1-year study in moderately IGFD children with ISS who were randomized to a 1-year observation or to IGF-I-based GH dose titration treatment was recently reported [48].

The results of these studies demonstrated that there is a large variability in the growth response of both GHD and ISS children to GH therapy that is dependent on a variety of factors including the degree of GHD and IGFD. Targeting higher IGF-I levels results in better growth. These studies also indicate that both the dose of GH and the serum IGF-I levels achieved during GH therapy are critical determinants of treatment outcome. While children with severe GHD typically respond well to traditional low doses of GH, children with ISS have decreased responses compared to GHD, even when treated with higher doses, indicating their lower responsiveness. These studies demonstrated that IGF-based GH dosing is clinically feasible in both GHD and ISS patients, although GH dose requirements and auxological outcomes are distinct among these groups.

Predicting the Growth Response with Genetic and Proteomic/Metabolomic Markers – Potential Improvement and Extensions of Prediction Models

The distance between the genetic and proteomic/metabolomics markers and statural growth is quite large, and growth is regulated by a still poorly understood in-

terplay of genetic and environmental influences. Therefore it may well be that the predictive effect of such markers may be too small to overcome the background noise. Still, we wish to summarize various studies on their potential predicting effect.

Circulating IGF-I Level as Potential Predictor for Growth Response to GH Therapy

The measurement of circulating IGF-I levels for diagnosing GHD showed a specificity of 95% but a sensitivity of 70% [49]. The specificity is relatively low in adolescents, probably because of the absence of appropriate reference standards for age and pubertal stage for most IGF-I assays [50] (except for a Swedish assay [51]).

IGF-I and IGFBP-3 concentrations provide information about the severity of GHD and have been shown to improve the degree of variance explained if included in the multiple regression analysis [28, 52]. In one of the Gothenburg prediction models, the pretreatment IGF-I value was found to be as informative as the GH_{max} (in an arginine-insulin tolerance test) when used together with auxological variables [27]. However, whereas a significant inverse correlation between pretreatment IGF-I levels and the height gain during GH therapy is a common finding [53], it is impossible to establish a cut-off for pretreatment IGF-I values to identify the responders.

Another proposed approach is to use the IGF generation test to assess the ability of an individual to respond to long-term GH therapy by elevations of serum levels of IGF-I in response to a short course of GH. However, this test has not yet been adequately standardized, and, more importantly, studies of GH-induced production of IGF-I and IGFBP-3 in children with GHD showed considerable variability in responsiveness and overlapping responses between patients with GHD and GH insensitivity [54, 55].

IGFBP-3, IGF-I and GHR Polymorphisms

For three elements of the GH-IGF-I axis the possible predictive value of genetic variants for the growth response to GH treatment has been investigated: IGFBP-3, IGF-I and the GH receptor (GHR). Twin studies showed that 60% of the interindividual variability in circulating IGFBP-3 levels is attributable to uncharacterized genetic factors [56], and in fact associations were found with two polymorphisms in *IGFBP3* [57, 58]. The 1st-year change in height SDS in short SGA children was associated with IGFBP-3 SDS, TH SDS, IGF-I SDS, age, and C-202/C-185 haplotype, explaining 52% of total variation in the 1st-year growth response [58]. With respect to circulating IGF-I, the proportion of variance attributable to genetic

effects has been estimated at 38% [56], and there was a haplotype effect of the *IGF1* promoter on serum IGF-I concentration [59]. The common polymorphism of *GHR* (deletion of exon 3), which is associated with enhanced GH signaling in an in vitro cell system [60], has a mild effect of 0.5–1 cm/year [61, 62].

There are also interactive effects of various polymorphisms, for example, interaction of a microsatellite in the *IGF1* promoter region with the *GHRdel3* and -202 *IGFBP3* variants on treatment outcomes of children with severe GHD [63]. *IGF1* and *IGFBP3* genotypes explained 29% of the 1st-year growth velocity variability; *IGF1* and *GHR* genotypes explained 59% of AH minus TH SDS variability, and the *IGF1* (CA)19 allele is associated with less favorable short- and long-term growth outcomes after GH treatment. In TS an interactive effect was demonstrated of *GHR-exon 3* and -202A/C *IGFBP3* on the treatment effect [64].

These studies suggest that various gene variants have an effect on growth response to GH treatment, and might theoretically improve prediction models. However, the functional relevance of the variants under investigation is uncertain.

PREDICT Study

The ongoing PREDICT study was conceived with the intention of evaluating whether single nucleotide polymorphisms (SNPs) in approximately 100 growth-related genes and/or gene expression profiles in whole blood mRNA might associate with early changes in serum IGF-I and other GH-dependent biomarkers, and then changes in growth over each year up to 5 years in prepubertal children with GHD and TS. The approach to analysis for the SNPs has been to first assess the association of a particular genotype or allele to auxological and biochemical outcomes. The second step has been to categorize the outcome variables into high/intermediate/low responders, and to identify SNPs that associate with these categories and are present in a reasonable percentage of the population.

Preliminary analyses have shown that: (1) SNPs and gene expression profiles associated with biomarker changes and growth in general differ between GHD and TS [65]; (2) genes associated with growth in general differ between year 1 and subsequent years, suggesting that genetic influences on CUG may differ from those on maintenance growth, and (3) significant SNPs are not confined to the classical GH-IGF pathways but do include genes controlling cell cycle, intermediary metabolism as well as transcription factors.

NESTEGG Study

The aim of the multinational Network of European Studies in Genes in Growth (NESTEGG) is to investigate whether small genetic variations (SNPs) in ten growth-related genes might explain the phenotype of 1,437 children (345 SGA-short, 288 SGA-catch-up, 410 ISS and 394 controls). A preliminary analysis has shown that several SNPs in various genes are associated with growth parameters and response to GH treatment [De Graaff et al., in preparation].

Biochemical Parameters and Proteomics

Prediction models of response on GH treatment have mainly been based on auxological data [30] or adding well-known biochemical parameters such as GH_{max} from a stimulation test or spontaneous secretion profile, IGF-I SDS, IGFBP-3 SDS or leptin at baseline [34]. Short-term changes of bone markers may be a complement to the classical prediction models [28]. In theory, a pharmacoproteomic approach to identify new biomarkers might improve the accuracy of previous prediction models.

In a study using proteomic techniques on 19 good responders and 32 poor responders out of 546 GH-treated prepubertal children [66], transthyretin (pre-albumin) and apolipoprotein A-II (component of HDL cholesterol) were found to change during the first treatment year. The levels of these markers decreased during treatment in the good responder group, whereas transthyretin decreased and apolipoprotein A-II remained unchanged in the poor responder group.

In the Swedish trial on the effect of individualized GH dosing [36], the predictive power of proteomic patterns before GH treatment for explaining the change in height SDS, bone mineral content (BMC), bone mineral density (BMD) and body composition was investigated. Apolipoprotein A-I, monomeric and dimeric apolipoprotein A-II, transthyretin, serum amyloid A-4 and hemoglobin β correlated with changes in height SDS and BMC/BMD [67], whereas changes in lean body mass and fat mass correlated with apolipoprotein C-I and with the previously mentioned peaks. GHD and ISS children showed an overlapping proteomic expression before GH start correlating to changes in body composition during treatment.

Health Economics and Outlook

Economic Value of a Data-Driven Approach to Treatment with GH in Children

Prediction models may not only be useful to improve the efficacy of GH treatment, but also to improve cost-

effectiveness. Based on the prediction model developed by Ranke and Lindberg [24], a cost-effectiveness model was developed to quantify the economic value of using this prediction model for evidence-driven decision-making in GH treatment [Kleintjens et al., submitted].

The model estimates the theoretical total GH costs and the total height gain in the presence and absence of evidence-driven treatment decisions. The analysis included all EU patients in the KIGS database for whom data were complete (5,333 patients with GHD and 1,173 patients with TS) and the results were applied to one country (Germany). Patients were segmented into three different responder groups: high responders ($>+1$ SDS for the reference population, average responders (between -1 and $+1$ SDS), and low responders (<-1 SDS), which included patients with low compliance, and patients who did not respond to GH. The economic analysis assumed that this segmentation would allow physicians to tailor dosage to the individual patient's needs or even to discontinue therapy when it is not effective.

This analysis showed that by adopting this approach it may be possible to substantially reduce the total GH drug use and expenditure, while the average growth outcomes in the treated population would remain unaffected [Kleintjens et al., submitted].

How Can Growth Prediction Models Influence Long-Term Treatment Strategies with GH?

Growth prediction models can in principle also be used to guide treatment decisions by estimating the dose needed to realize a specified amount of growth [30, 34, 44, 68]. However, since current prediction models contain only a single term for the GH dose, they are limited to prediction of growth for a fixed dose during the whole treatment period under consideration.

Recently, Ranke et al. [69] have validated the sequential use of annual KIGS prediction models for up to 4 years of prepubertal growth in patients with TS and GHD. Since each annual model contains its own term for the GH dose, this prediction system can be used to simulate growth when the dose is changed along the course of treatment. This could allow for maximizing growth for a given amount of GH, or for minimizing the amount of GH for a given growth outcome. Figure 5 illustrates three possible scenarios to increase the height SDS from -2.5 to -1.5 SD over a 4-year period in a patient with TS. The amount of GH needed with the 'first high then low dose' scenario is up to 20% lower compared to the 'first low then high dose' scenario, while the cost of the fixed average dose scenario is in between these. The main advan-

Fig. 5. A simulation of three scenarios to realize a relative growth of +1 SDS in a TS patient using different dosage schemes. The percentage indicates the total amount of GH administered over 4 years, relative to the reference treatment. Approximate doses used in this simulation are: low 0.17, average 0.22, above average 0.27, and high 0.35 mg/kg/week (24, 31, 39 and 50 µg/kg/day, respectively).

tage of the first scenario is the realization of most of CUG during the 1st year of treatment, when the response to GH therapy is larger. This property is well known from clinical practice, and can also be deduced from the KIGS models using algebraic substitution.

Flexible growth prediction models that allow variable doses during subsequent treatment years are a promising development for individualized treatment, but require further validation [69]. KIGS models are based on patients that received a fixed dose for the whole prepubertal treatment period, and their validity for treatment schemes with variable dosage should be assessed. This can be done in existing patient databases, given that changes in dose did not depend on the outcome, or in a randomized controlled bioequivalence trial. Ideally, these long-term prediction models should also include near AH. When considering alternative treatment schemes, safety should always be the foremost issue. In this respect, the simulation described in this paragraph was conducted within the current approved limits for GH in Europe.

Conclusion

A GH treatment regimen based on a fixed dose per body size leads to a variable growth response, of which approximately 50% can be predicted by easily available patient and treatment characteristics. For the Gothenburg and Cologne models, needing additional information on variables that may be less easily available, higher

percentages were reported. In theory, the variation in the growth response to treatment can be reduced by using any of the available prediction models in a prospective fashion, but so far this has only been proven for the Gothenburg model. When used after the 1st year of treatment, comparing the attained growth response with the predicted growth response can lead to adaptation of the dose, according to the observed individual responsiveness. Thus, prediction models may offer an improvement in the treatment with GH in addition to available tools and subjective judgment. Efforts are ongoing to find proteomic or genomic predictors in order to possibly improve the presently available clinical prediction models. Two analyses have suggested that it is possible to use the KIGS models for the whole growth period to compare different treatment strategies, and find strategies with an improved outcome in terms of both efficacy for the individual child and for health economics, compared to the traditional fixed dose regimens. User-friendly and easily available computer programs would facilitate the clinical usefulness.

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J.M.W. has served on an advisory boards for Tercica, Ipsen, Pfizer, Prolor, Teva and Biopartners, and has received speaker honoraria from Pfizer, Lilly, Ipsen and Ferring. M.B.R. has served as consultant to Pfizer, Inc. N.Y. and has received speakers honoraria from Pfizer, NovoNordisk and Ipsen. K.A.-W. has received lecture fees from Pfizer, unrestricted research grants from Pfizer (until 2005) and grants for the Swedish National GH Registry from NovoNordisk, Ipsen and Merck Serono. A.C. has received lecture fees, consultant fees, and grants from Pfizer, Lilly, Ipsen, NovoNordisk and Merck Serono. R.G.R. is a consultant for Ipsen, Prolor, Versartis and Teva. B.K. has received consultation and lecture honoraria from Pfizer, NovoNordisk, Ipsen and Merck Serono and served on advisory boards for Pfizer and NovoNordisk. E.S. received honoraria or consultation fees from Bayer, Eli Lilly, Ferring, Ipsen, Pfizer, Merck Serono and NovoNordisk. L.A. has served on an advisory board for Pfizer and has received speaker honoraria from Pfizer and NovoNordisk. A.H.-K. has received lecture fees, consultant fees and independent research grants from Ipsen, NovoNordisk and Pfizer and is member of the Global Norditropin Advisory Board and Strategic Advisory Board of KIGS/Pfizer. P.B. has received lecture fees, consultant fees and grants from Ipsen, NovoNordisk, Merck Serono, Lilly and Pfizer and he chairs the Ipsen IGFD registry data review committee and SECC (Short Stat-

ure Expert Committee). H.J. and W.F.B. are employees and stockholders of Eli Lilly & Co. L.A.S. has received research grants and honoraria from Pfizer and Versartis, and is an advisor for Merck Serono and NovoNordisk. P.C. is a consultant for NovoNordisk and Teva. S.C. has received lecture fees, consultant fees, and grants from Pfizer, Lilly, Ipsen, NovoNordisk and Merck Serono. C.D. has received lecture fees, consultant fees and participated in funded research with Lilly, Merck Serono, Pfizer, NovoNordisk and

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