Identification and management of poor response to growth-promoting therapy in children with short stature

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IDENTIFICATION AND MANAGEMENT OF POOR RESPONSE TO GROWTH-PROMOTING THERAPY IN CHILDREN WITH SHORT STATURE

Short title: Poor response to growth-promoting therapy

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Summary

GH is widely prescribed for children with short stature across a range of growth disorders. Recombinant human (rh)IGF-1 therapy is approved for severe primary IGF-I deficiency – a state of severe GH resistance. Evidence is increasing for an unacceptably high rate of poor or unsatisfactory response to growth-promoting therapy (i.e. not leading to significant catch up growth) in terms of change in height standard deviation score (SDS) and height velocity (HV) in many approved indications. Consequently, there is a need to define poor response and to prevent or correct it by optimizing treatment regimens within accepted guidelines. Recognition of a poor response is an indication for action by the treating physician, either to modify the therapy or to review the primary diagnosis leading either to discontinuation or change of therapy. This review discusses the optimal investigation of the child who is a candidate for GH or IGF-1 therapy so that a diagnosis-based choice of therapy and dosage can be made. The relevant parameters in the evaluation of growth response are described together with the definitions of poor response. Prevention of poor response is addressed by discussion ***of strategy*** for first-year management with GH and IGF-1. Adherence to therapy is reviewed as is the recommended action following the identification of the poorly responding patient. The awareness, recognition and management of poor response to growth-promoting therapy will lead to better patient care, greater cost-effectiveness and increased opportunities for clinical benefit.

Introduction

The management of short stature comprises many challenges, not least the options of appropriate hormonal therapies and their administration in regimens that are most beneficial. GH therapy is licensed by the European Medicines Agency (EMA) for treatment of GH deficiency (GHD), Turner syndrome (TS), short stature related to birth size small for gestational age (SGA), Prader-Willi syndrome, *SHOX* deficiency and chronic renal insufficiency. In the USA, the Food and Drugs Administration (FDA) has in addition approved GH therapy for idiopathic short stature (ISS) and Noonan syndrome. Recombinant

human (rh)IGF-1 therapy is licensed by the EMA and FDA for treatment of severe primary IGF-I deficiency, characterized by specific criteria.[1]

As experience with different treatment regimens accumulates, it is clear from reports of GH treatment that individual first-year height responses vary considerably [2–4] even with individualized treatment regimens.[5] Poor short-term response is also translated into an unsatisfactory gain in adult height.[6]

This review addresses the identification and management of poor or unsatisfactory growth responses in children with licensed indications for growth-promoting therapy. We discuss the investigation of short stature aimed at establishing a diagnosis, the parameters of response, factors predicting response, decisions relating to start of therapy, the problem of adherence and finally the management of the poorly responding patient.

The continuum of growth disorders

Growth disorders exist across a continuum ranging from extreme GH sensitivity to extreme GH resistance.[1,7] An extensive review of the different ***genetic*** growth disorders in this continuum has recently been published.[8] An inherent component of the continuum is the variation in responsiveness to GH therapy. It is now well recognised that children with severe GHD are highly responsive to GH replacement[4,9] and patients with less severe or questionable GHD often respond less well. In recent reports of GH responses, there were no differences in response between subjects with less severe GHD and those with 'normal' GH secretion labelled as having ISS.[4,10] A strict distinction cannot be drawn between GHD and ISS and as the continuum of responsiveness to GH varies across and within diagnostic groups, the relevance of relating a sufficient response to a specific diagnosis can be questioned.

In disorders of GH resistance, the effect of GH therapy further decreases and rhIGF-1 treatment is indicated.[11,12] Criteria for lack of response to rhIGF-1 similarly need to be

defined.

Clinical assessment and investigations aimed at identification of a primary diagnosis

Clinical assessment and investigation are important because the choice of therapy and dosage should be related to the primary diagnosis. The predicted response depends on a number of variables identified at initial assessment.

History and physical examination

The history and physical examination are essential[13,14] and attention should be paid to premature and/or SGA (low birth-weight or birth-length) birth. The presence of chronic disease should be considered and dysmorphic features should be documented. **Parental heights *are* relevant and known to be related to the response to GH.**

Hormonal status

The identification of genetic defects in the GH–IGF-axis[8] has underlined the importance of endocrine assessment including determination of serum IGF-I and GH secretion. ***Recently, a consensus on GH and IGF-I determinations was published.***[15] Measurement of IGFBP-3, acid-labile subunit (ALS) and GH binding protein (GHBP) may be considered, as may an IGF-I generation test and eventually molecular analysis for candidate gene defects.[8] Severe classical GHD should be diagnosed early in patients with neonatal symptoms of hypoglycaemia and prolonged jaundice, a characteristic growth pattern and possible additional pituitary hormone deficiencies. GHD in these children and in those with less severe idiopathic GHD (IGHD) are ***conventionally*** confirmed by a low IGF-I concentration and GH provocative testing with a GH cut-off set at 7 or 10 µg/l.

However, this cut-off leads to a separation between IGHD and ISS that lacks physiological evidence as indicated by similar responsiveness to GH treatment.[4] Furthermore, ***as many as 50% of GH-treated children with short stature, born SGA*** have low stimulated GH

concentrations.[4] Poor reproducibility and a high incidence of false ***subnormal*** responses to different pharmacological stimuli are further limitations of GH stimulation tests.[13,15] The difficulties in discriminating between IGHD and ISS or SGA were ***clarified by the study of Kriström[5] et al and in the report of Loche et al[16]*** who showed that 85% of IGHD patients with two stimulated peak GH values <10 µg/l and normal pituitary magnetic resonance imaging (MRI) had values of GH >10 µg/l when re-tested 1–6 months later.

Serum IGF-I levels are largely GH-dependent, but also influenced by age, pubertal development, malnutrition, chronic inflammation or hepatic diseases. A ***subnormal (<−2 SD)*** IGF-I concentration indicates GH testing should be performed but cannot take its place. Evaluation of spontaneous nocturnal GH secretion is used in a small number of centres and may have higher predictive value for the response to GH treatment, although this remains to be confirmed.[17]

If GH secretion is normal, IGF-I deficiency, provided chronic disease has been excluded, may be 'primary' (ie primary IGF-I deficiency) indicating GH resistance, with possible sites being the GH receptor, GH post-receptor signalling including defects in *STAT5b*, or the *IGF1* gene.[8] A defect of circulating IGF-I transport due to a mutation in the *IGFALS* gene may be a more frequent cause of primary IGF-I deficiency although growth retardation is milder.[18,19] To investigate GH resistance the IGF-I generation test may be helpful but the results are seldom clear-cut except in extreme GH resistance and the test should not be mandatory.[8,20]

Radiological assessment

MRI of the hypothalamic–pituitary region must be performed when GHD is diagnosed, to exclude an organic cause. Skeletal survey is indicated for body disproportion and an x-ray of the left hand and wrist for bone age, although not diagnostic, may be relevant to management.

Genetic assessment

In certain children, the family history and clinical features may suggest a single gene defect. Key features are the presence of one or more of the following: a positive family history, parental consanguinity, severe growth failure, facial dysmorphism caused by IGF-I deficiency due to extreme GHD or GH resistance, immune deficiency, intrauterine growth retardation, deafness and microcephaly.[21] Single gene defects in the GH–IGF-I axis may involve hypothalamic–pituitary development, GH secretion, GH binding to its receptor, intracellular GH signalling and IGF-I synthesis and action. The available genetic techniques currently in use in growth assessment are shown in Fig. 1.

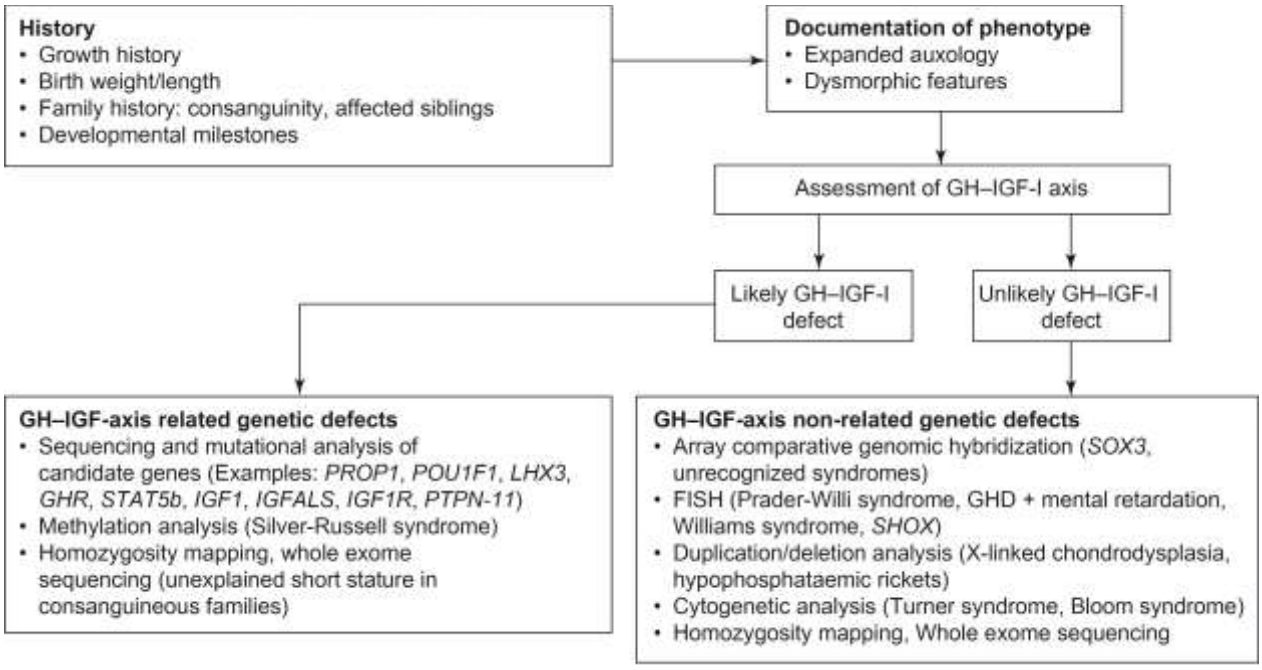

Fig. 1 – Scheme for genetic investigation of short stature with available genetic techniques and examples of disorders for which they are appropriate[21,22]

Relevant parameters in the evaluation of GH response

A number of factors are key determinants of the pattern of response to GH treatment.[6,9,17] Assessment of responses to IGF-I therapy will be discussed later. In this section, we consider the pre-pubertal response to GH treatment since the short-term height response in a pubertal subject may be difficult to interpret. ***Growth hormone dose*** and growth response during the first year of GH therapy ***are*** strong predictors of final height outcome. [9,17,23-26] In pre-pubertal

GH-treated children with IGHD, a first-year height increase of 0.5 standard deviation score (SDS) corresponds to an average final height gain of approximately 1.0 SDS.[27] A number of possible growth response parameters are considered.

Growth during the first year of GH therapy: parameters of response

Increase in height SDS and height velocity (HV)

Increase in height SDS is perhaps the most relevant parameter for the patient and parents, since deviation in growth relative to peers and the demonstration of how the patient's height will change with therapy is clinically and psychologically important. This also impacts ***on*** adherence. The increase in height SDS can easily be calculated. HV is also easy to discuss with the patient and parents. However, the actual increase in cm/year (ie, annualized HV) that results in a gain in height compared with peers is dependent on age. Both HV and increase in height SDS are endpoints in growth prediction models and first-year HV is the standard endpoint in clinical trials.

HV SDS and increase in HV

Expressing the HV SDS of a child on GH with reference to healthy children is hampered by the lack of reference data. Available data are based on longitudinal studies in small numbers of healthy children or on cross-sectional data. HV SDS in the first ***and subsequent years*** of GH treatment may have a non-linear relationship with age.[3]

Determinations of increase in HV, comparing annualized HV during the first year on GH with that of the pre-treatment year, are often restricted by absence or lack of reliable data. HV in a healthy child changes over time and pre-treatment data should be derived from a full year.[28] Given the caveats of these two growth response measures they will not be discussed further in this article.

Age-dependency of responses

Increases in height SDS and HV during the first year on GH treatment ***in different diagnoses (Table 1)*** are strongly age-dependent.[3,4,10] This ***age-dependency*** is largely explained by the physiology of normal linear growth. Firstly, the equivalence of 1.0 height SDS is approximately 3, 5 and 6 cm at ages of 2, 7 and 11 years, respectively.[35] Although mean heights at given ages differ in different populations, the width of 1.0 height SDS is relatively stable across populations, at least prepubertally (unpublished observations). Secondly, HV values in healthy children also change with age, with the young child growing much faster. Normal mean HVs are approximately 9, 6 and 5 cm/year at ages of 2, 7 and 11 years, respectively. Therefore, a higher proportion of children with a given diagnosis starting GH at a younger age will gain 1.0 height SDS and have ***higher HV values*** during the first year of treatment compared with children starting GH at an older age.[4] Several clinical trials and post-marketing registries report data on mean (± SD) or median (percentiles) first-year height responses or gain in final height in GH-treated children (Table 1). These studies consistently report better responses when treatment is started at an early age – the number of years of pre-pubertal GH treatment strongly predicting final height.[23-26,33]

References from NCGS and KIGS databases

Recently, age, sex and diagnosis-specific references have been derived from large numbers of GH-treated pre-pubertal children registered in the National Cooperative Growth Study (NCGS) (n=7000) and Pfizer International Growth Database (KIGS) (n=8500).[3,10] Reference data of increase in first-year height SDS or HV during GH therapy allow assessment of height response in patients with IGHD, organic GHD (OGHD), ISS and TS.[3] ***In the NCGS cohort[3] the patients have not been divided according to the severity of GHD, as they were in the KIGS cohort.***[10] ***In the later cohort,*** reference data exist for idiopathic GHD, separated into severe (peak GH <5 µg/l) or less severe (peak GH 5–10 µg/l) deficiency, TS or SGA.[10] ***These references reflect the patient selection and the prescription and management routines of the past. The usefulness of such references, therefore, may be limited if these routines***

change due to current focus and discussion of poor response and its management. The mean first-year HV curve of subjects with less severe IGHD treated with GH reported by Ranke *et al*. was superimposable on the mean HV −1.0 SD curve for IGHD reported by Bakker *et al*. (Fig. 2A). This may be explained by the 40–50% larger GH dose used in the USA and that a greater proportion of children with severe GHD with higher responsiveness were included in the Bakker series.

Response related to diagnosis

Arguably, a major limitation of the age-related and sex- and diagnosis-specific references is that none includes all GH indications. However, the variation in response within each diagnostic group largely overrides the difference in mean HV curves among the different diagnoses (Table 1). For example, the KIGS data[10] show that the mean HV curve of subjects with severe IGHD only differs from those of less severe IGHD and SGA by approximately 1.5 cm/year over the entire age range (Fig. 2B). This difference is within the variability in response for each diagnosis (the width of one SD is ~2.5 cm/year for severe GHD and ~1.5 cm/year for less severe GHD and SGA). It is therefore debatable whether there is a need for more than one reference, to which any given patient, independent of diagnosis could be compared. The response to GH in severe ***GHD could*** be used as such a reference. This approach to define poor response would be consistent with the concept of a continuum of responsiveness in the GH–IGF-axis. Importantly, it also acknowledges that in a higher proportion of patients with less severe GHD, SGA, ISS and TS sensitivity to GH is decreased and the response to GH is poor.

Definitions of poor response

If diagnosis-, sex- and age-specific references are not used, another strategy to define the minimal acceptable growth response is required. Several diagnosis-, age- and sex-nonspecific definitions of poor first-year GH treatment response have been proposed. These include an increase in height SDS <0.3 or <0.5, an increase in HV <3 cm/year and an increase in HV

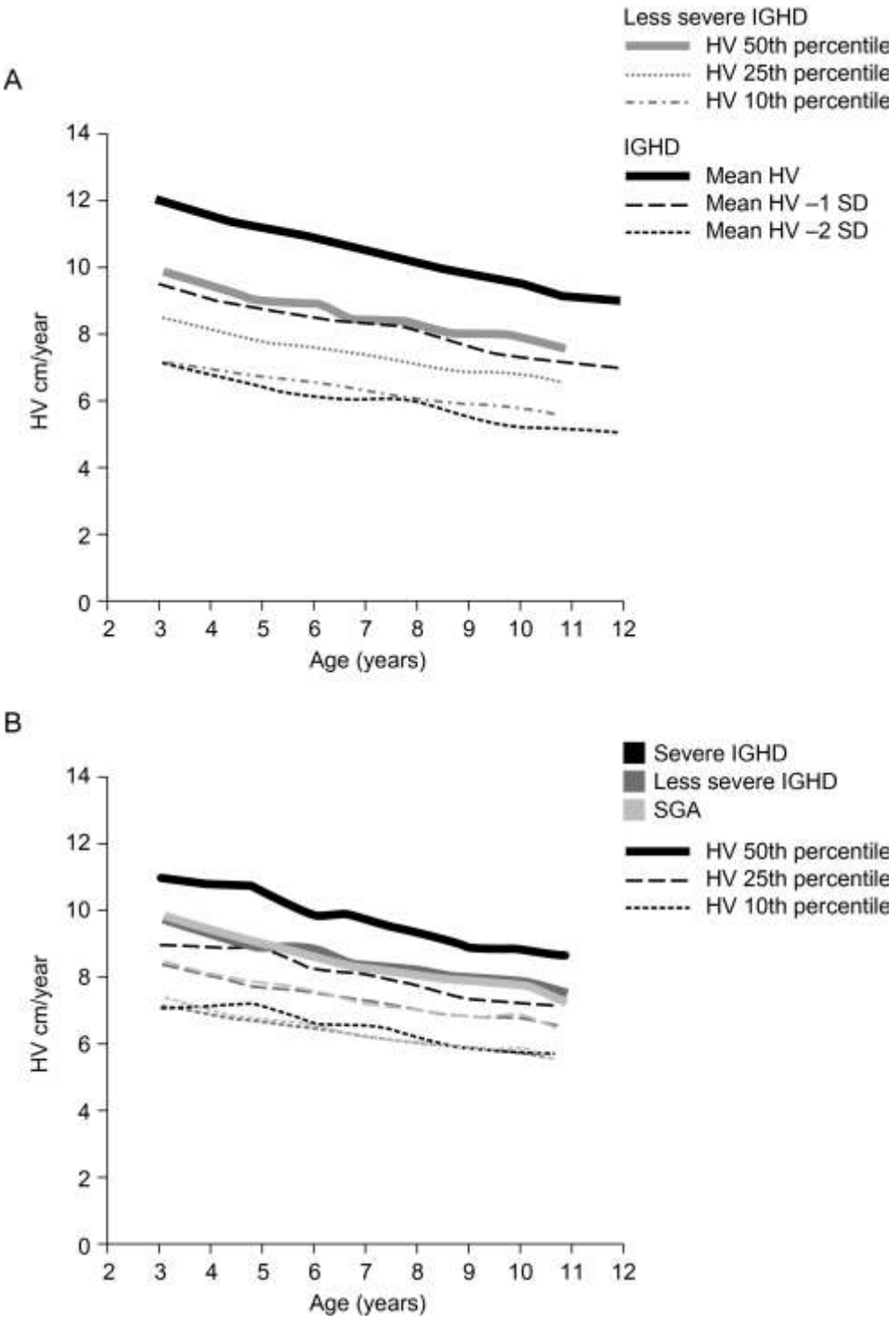

Fig. 2A – HV during the first year on GH therapy in pre-pubertal children with less severe IGHD (stimulated peak GH 5–10 µg/l) registered in the KIGS database, represented by the 50th, 25th and 10th percentiles (grey lines), derived from the report by Ranke *et al.*[10] Superimposed are data on HV in patients with IGHD (peak GH not defined) registered in the NCGS database, represented by the mean, mean HV –1 SD and mean HV –2 SD (black lines) derived from the report by Bakker *et al.*[3]
Fig. 2B – HV data in less severe IGHD (grey) are superimposed with data from children with severe IGHD (stimulated peak GH <5 µg/l; black) and SGA (light grey), adapted from Ranke *et al.*[10] IGHD, idiopathic growth hormone deficiency; HV, height velocity; SGA, small for gestational age.

SDS <+1 SD compared with healthy children.[10,14,36–38]

The first study to define the proportion of patients that did not exceed these cut-offs was reported recently.[4] Responses to GH were analyzed in 456 short, pre-pubertal Nordic children and the numbers of children with a first-year increase in height SDS <0.5 ranged from almost 30% in IGHD (including those born SGA) and OGHD, a similar percentage in ISS, almost 50% in SGA and almost 60% in TS and skeletal dysplasia (Fig. 3). After excluding those with severe IGHD (peak GH <3 µg/l), IGHD patients did not differ in their mean HV response versus those with ISS or SGA. Furthermore, responsiveness to GH in SGA patients with IGHD (peak GH <10 µg/l) was not different from patients with less severe IGHD.[4]

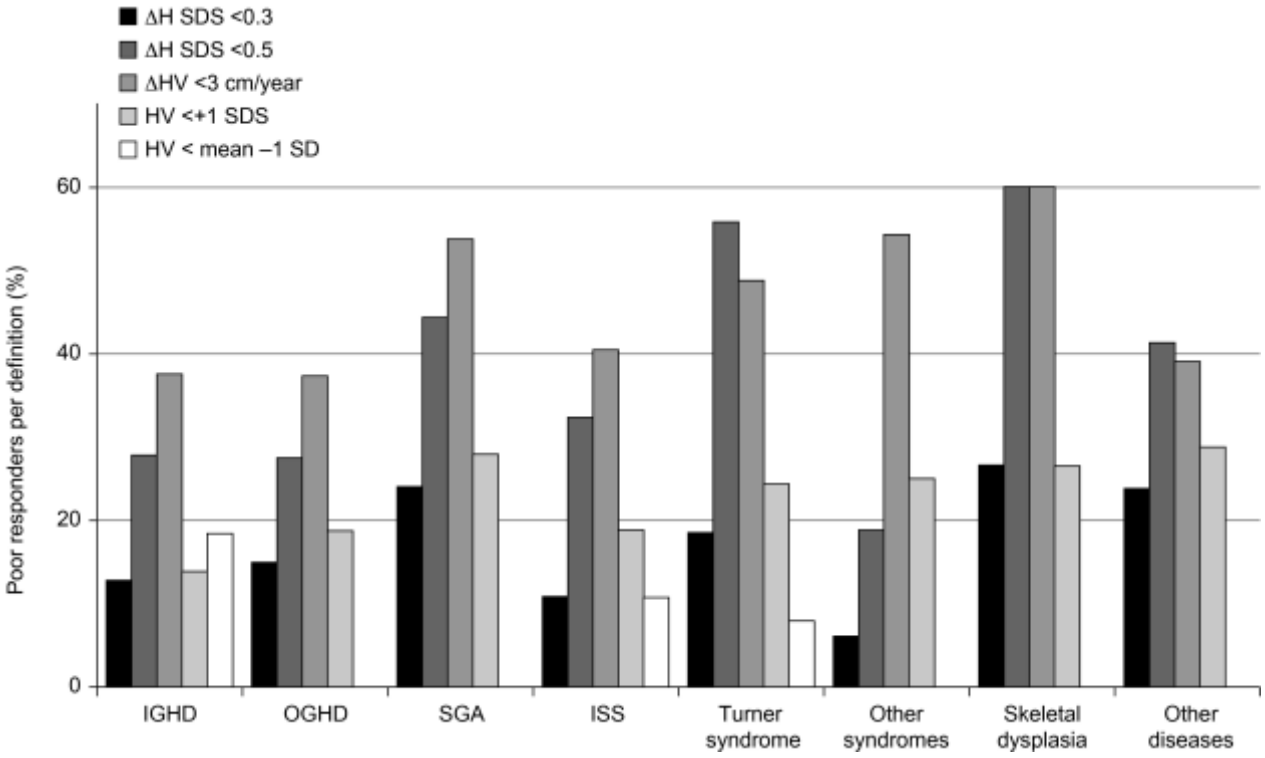

Fig. 3 – Proportion of poor responders after 1 year of standard GH therapy in 456 short pre-pubertal children according to different definitions in each diagnostic group as reported by Bang *et al*.[4] HV <mean −1 SD of the first year on GH response according to Bakker *et al*.[3] Bakker data only available for IGHD, ISS and Turner syndrome. HV, height velocity; IGHD, idiopathic growth hormone deficiency; OGHD, organic growth hormone syndrome; SGA, small for gestational age; ISS, idiopathic short stature. Reproduced with permission from S. Karger AS, Basel. © 2011.

Consensus on the definition of a poor or inadequate first-year GH response, however, is lacking,[39] as indicated at recent consensus workshops on ISS[14] and SGA.[40] Bakker *et al*[3] suggested that patients with a first-year HV < mean HV −1.0 SD for that sex and diagnosis should be labelled as poor responders.[3] Similarly, Ranke argued, that using the same cut-off, a poor response equals a gain in height SDS of <0.4 in a patient with severe GHD and an increase in height SDS of <0.3 in patients with less-severe GHD, girls with TS, or SGA subjects.[10]

However, at ages 3 to 8 years, an increase in height SDS of <0.3 is within the normal variation of height measures observed over a 1-year period.[41] A sufficient height response to GH treatment should lead to catch-up toward the target height[42] and must ***ideally*** be distinguishable from the normal variation in height in healthy children, and therefore the cut-offs suggested by Bakker *et al*. and Ranke *et al*. may not identify all children with a true poor response to therapy.

Definition of clinical benefit

An acceptable treatment response should equate to or exceed a level at which ***a measurable*** clinical benefit for the patient has been shown. ***In conditions where the main objective is to improve short-term height and normalize adult stature, the impact on quality of life should be considered. New data on quality of life in children receiving GH therapy have recently been published.***[43] In severe GHD, normalization of body composition and metabolism are also a goal of treatment.

Biomarkers of GH response

Short-term markers of growth response such as IGF-I, IGFBP-3 and bone matrix components may improve predictions of first-year response to GH treatment.[5,23] Basal and short-term changes in IGF-I and IGFBP-3 are related to the first-year height SDS and HV changes in subjects with GHD.[4,29] ***Markers of bone turnover such as alkaline phosphatase, bone***

alkaline phosphatase, osteocalcin and procollagen type 1 C-terminal propeptide, and urinary markers of bone resorption increased significantly during the first year of GH therapy in GH deficient patients and formed part of a prediction model of GH response[44] ***. However these early markers of response to GH treatment are not used routinely.***[45]

Prediction of response to GH therapy

Growth prediction models

Over ten years ago, the relative inflexibility of GH treatment regimens and the simplicity of the modalities used to derive them, led to the introduction of mathematical models aimed at predicting growth responses in individual patients.[9,17] Such models ***attempt*** to account for the definable variability of responsiveness so that clinicians ***can*** adapt GH doses to individual patients.[6] Prediction models for the first-year HV as well as the total height gain were published, for patients with GHD[9,17] TS,[46] or SGA[47] and for patients with varying degrees of GH secretion or ISS.[17,23,24]

Based on multiple regression analyses, these models have identified a number of factors that correlate with growth. For example, chronological age, birth weight SDS, height SDS, ***height SDS minus target height SDS,*** GH peak during provocative tests and dose of GH, are key variables associated with the first-year HV.[9,17] Biochemical variables such as baseline IGF-I[17] and leptin[23] have added to the prediction of response. Prediction models derived from the large KIGS database explain approximately 60% of the variability of response to GH therapy in patients with GHD and 40% in subjects with ISS.[6] ***We believe that prediction models should be used where possible to calculate the optimal starting GH dose and to help in dose adjustment where indicated in different diagnoses.***

Pharmaco-genomic and pharmaco-proteomic studies

The addition of pharmaco-genomic analyses to the above variables may increase the accuracy

of prediction models. ***Results following the addition of genomic data to prediction model calculations and evidence of their enhancement of model performance are keenly awaited.*** For example, the presence of the exon 3 deletion polymorphism in the GH receptor may enhance the response to GH therapy in some subjects,[48] notably those with severe GHD[30] as may the presence of the -202 A polymorphism in the *IGFBP-3 promotor* gene.[49] Patterns of changes in gene expression in peripheral blood mononuclear cells have been reported during GH therapy in GHD subjects potentially leading to the ability to further predict GH responsiveness.[50] Such pharmaco-genetic investigations have great potential.[51]

In addition, an increasing number of proteomic approaches can be expected such as that used by Hellgren *et al*[52] identifying new potential GH responsive proteins such as transthyretin and apolipoprotein A-II. So far, pharmaco-genomic and pharmaco-proteomic markers have **not been formally validated. However, it appears that they may add only minor improvements to existing** prediction models. Ongoing genetic studies such as the EPIGROW study (http://clinicaltrials.gov/ct2/show/NCT00710307) by Ipsen or the PREDICT study (http://clinicaltrials.gov/ct2/show/NCT00699855?term=predict+GH&rank=2) by Merck Serono may contribute new data on genomic markers of GH response.

Management of the first year on GH therapy

Discussion of decision to treat and expected response

Before the start of GH treatment, the parents and child should be fully informed about the underlying condition, the probable pathophysiology of growth retardation, the rationale for GH therapy and the evidence-based expected growth response. This should be based on a prediction model ***calculation and*** should reflect the large variability in response among individuals inherent in the continuum in GH sensitivity. Likely duration of therapy and the level of response at which discontinuation of treatment will be decided must also be

discussed. The decision to start and stop treatment should be made in consultation with the patient and parents. Interestingly, data in the KIGS database on why GH treatment is being stopped do not include "poor response" as an option.[53] A recent consensus statement on the use of GH in ISS emphasized the importance of discouraging the expectation that taller stature will improve quality of life.[14]

Dose of GH

The starting dose of GH depends on the diagnosis of the condition and is usually calculated according to weight or body surface area. The recommended GH dose for each approved indication ***may differ between countries and reflects the responsiveness to GH in the condition being treated.*** However, the recommended dose does not routinely consider the variation in responsiveness within each diagnosis spanning the continuum of growth disorders. In cases where high GH sensitivity is expected including subjects with extreme GHD or obesity such as craniopharyngioma patients, a lower starting dose is recommended. Although differences in dosing during the first year of GH therapy may exist among countries and centres,[54] there is evidence for adherence to the recommended doses within each indication.[4] If assessment after 1 year of treatment, or after 6 months if there is no increase in height SDS, shows that the growth response is inadequate, the dose of GH may be increased. In some indications such as SGA[40] and ISS,[14] the recommended maximum dose of GH may be used from start of treatment or the dose may be increased as necessary. Comparison of GH dosing approaches, involving discontinuous high-dose or continuous lower-dose regimens, for example in SGA subjects[55] concluded that a broad spectrum of GH regimens is effective.

In some situations, such as ISS, concern has been raised that higher GH doses ***of up to approximately 70 µg/kg/day*** advance bone age and pubertal progress,[56] but this has not been confirmed.[57] There are no definitive data concerning the long-term safety of doses higher than 50 µg/kg/day in children with ISS. A GH dose of 70 µg/kg/day was approved in the USA for treatment of GHD in puberty but this regimen is only used by one third of centres.[58] In

December 2010, the EMA issued guidance (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/12/news_detail_001167.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1) not to exceed a GH dose of 50 µg/kg/day based on preliminary data from a French post-marketing registry study, now published[59] in addition to data from Belgium, the Netherlands and Sweden.[60] However, following a review by the EMA's Committee for Medicinal Products for Human Use (CHMP) of available data on the safety of somatropin (GH)-containing medicines, including data from clinical trials, registries and observational studies, as well as reports of side effects from post-marketing surveillance, it was recently concluded that the benefit–risk balance of somatropin-containing medicines remains positive when used in the licensed indications at the approved doses (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/somatropin_107/WC500119354.pdf). It was recommended that the maximum recommended daily dose should not be exceeded

Monitoring during GH therapy

During the first year of GH therapy, children should be seen at 3 to 6 monthly intervals for assessment of growth, puberty, ***mood, body composition and to support compliance with therapy.*** These visits may be used to judge response to GH but growth response cannot be reliably assessed at an interval shorter than 1 year[28,61] GH dose adjustments during the first year of treatment may not have been as common in the past and may be less frequent in some countries[4] than in others.[58]

IGF-I is a short-term biomarker of efficacy as well as a marker for adherence to therapy. The significance of abnormally elevated IGF-I levels in children on GH therapy remains unknown. However, it is recommended to consider GH dose reduction if IGF-I is repeatedly above the upper limit of the normal range or +2.5 SDS.[14] Deciding the starting GH dose based on the Swedish prediction model resulted in GH doses from 17 to 100 µg/kg/day but did not

decrease the occurrence of serum IGF-I levels above the normal range.[5] However, this approach did result in a smaller variability in height responses during the first 2 years of GH therapy compared with conventional dosing. In SGA, the recommended maximum dose of 0.067 mg/kg/day increased IGF-I far above the normal range[62] although the height response was not similarly increased.

Monitoring of parameters of glucose metabolism may be performed although there is little evidence for its clinical relevance except in children with chronic inflammation receiving glucocorticoid therapy[63] or in conditions such as TS and SGA or cases of a family history predisposing to diabetes.

rhIGF-1 therapy

Severe primary IGF-I deficiency (height <−3 SDS, serum IGF-I <2.5th centile in EU and <−3 SDS in USA, GH normal) is a licensed indication for the use of rhIGF-I in Europe and the USA.[1] Given the rarity of this condition, patients should be managed by an experienced paediatric endocrinologist. Patients with severe primary IGF-I deficiency generally do not achieve the same first-year HV with rhIGF-1 treatment as those with severe GHD treated with GH because of the additional disruptions of the IGF-I system.[64] Subcutaneously administered exogenous IGF-1 does not compensate for the lack of IGF-I independent actions of GH at the growth plate and the pharmacokinetics of IGF-1 is affected by the deficiencies of the GH-dependent ALS and IGFBP-3 carrier proteins. The response to treatment with rhIGF-1 should be evaluated according to the recommendations given for GH treatment above, although the severity of the growth retardation, projected adult height and lack of alternative therapy may be considered. On average, responses to rhIGF-1 treatment are better when treatment is started at a lower age and the response is dose-dependent.[11] However, the patient with extreme IGF-I deficiency does not appear to be more sensitive to rhIGF-1 therapy[11] and no relationship between ***change in HV*** and basal or stimulated serum IGF-I has been seen.[12]

Adherence to GH therapy and its impact on response

Poor adherence may contribute to the variability in response to GH therapy although it may be of less concern during the first year of therapy in pre-pubertal children.[65] In the context of adherence, serum IGF-I is the most commonly used biomarker and its response to treatment is well characterized although the relative changes are smaller in disorders without GHD.[2]

Adherence to GH therapy involves daily and sometimes painful injections and physicians prescribing GH have to educate patients and their families about the necessity, context and objectives of the therapy. Individual psychological strain of treatment is also likely to affect adherence, and ethnic and socioeconomic factors and the educational level of families are also relevant.[66,67] Adherence was reported to be better in children who chose the injection device themselves, self-injected and were trained by hospital staff.[68]

Impact of adherence on growth response

The impact of adherence on outcome to GH treatment has been studied showing that non-adherence impaired the growth response (Fig. 4).[65,66,69] It remains unclear whether adherence differs between the various indications for GH treatment.[67] Most studies of adherence with GH may not show an accurate picture of the attitudes of the patients and their families.[67] Informed consent and shorter intervals between patient visits as practised in GH treatment studies may improve motivation and reinforce long-term adherence.

A number of GH injection devices are available and the choice of product should be made on an individual basis taking into consideration therapeutic need and the likelihood of adherence to treatment.[68] Adherence may be improved by the use of GH injection devices that include computerized pen-systems with skin sensors documenting the dose and frequency of injections. ***However, the distinction between poor growth due to non-compliance and non-responsiveness may be difficult.*** A close link with an endocrine specialist nurse will also

facilitate good education to convince and empower patients to use self-care strategies to achieve their treatment goals.[67]

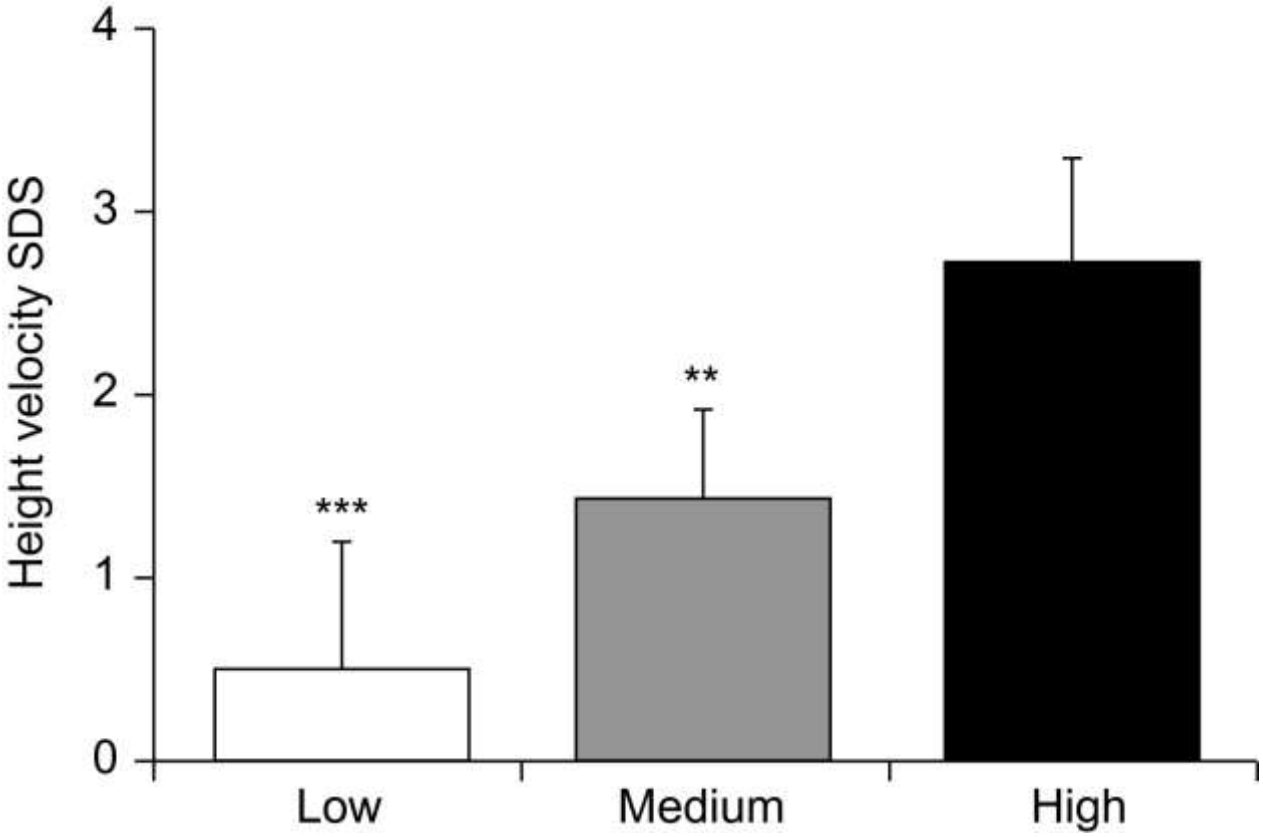

Fig. 4 – Height velocity standard deviation scores (HV SDS) over 6–8 months according to the level of compliance with GH treatment: High (*n=30*), missed ≤1 dose/week, Medium (*n=51*) missed >1 and <3 doses/week, and Low (*n=29*) missed ≥3 doses per week. Data are mean ± SEM. ** p<0.01, *** p<0.001 vs High.[66]

Management strategies for children with poor response to GH therapy

As a general rule, the response to GH therapy should be assessed following ***12 months*** of therapy (Fig. 5).[4,28,61] If a patient demonstrates a poor response, further evaluation of the diagnosis and indication for therapy is necessary. Several options for further management can then be considered. Repeated IGF-I measurements after 3 and 6 months of GH therapy may be used for GH dose titration. If initial biochemical parameters suggested the existence of GH resistance, ie low IGF-I with normal GH concentrations, IGF-I-based dose titration should yield a GH dose able to overcome such GH insensitivity. If this is not achieved, a disorder associated with GH resistance should be considered and rhIGF-1 therapy may be indicated if the patient fulfils the criteria of severe primary IGF-I deficiency. The mean first-year HV for

ISS patients with low IGF-I concentrations who were treated with rhIGF-1 for 1 year was similar to that reported for GH-treated pre-pubertal children with ISS.[12]

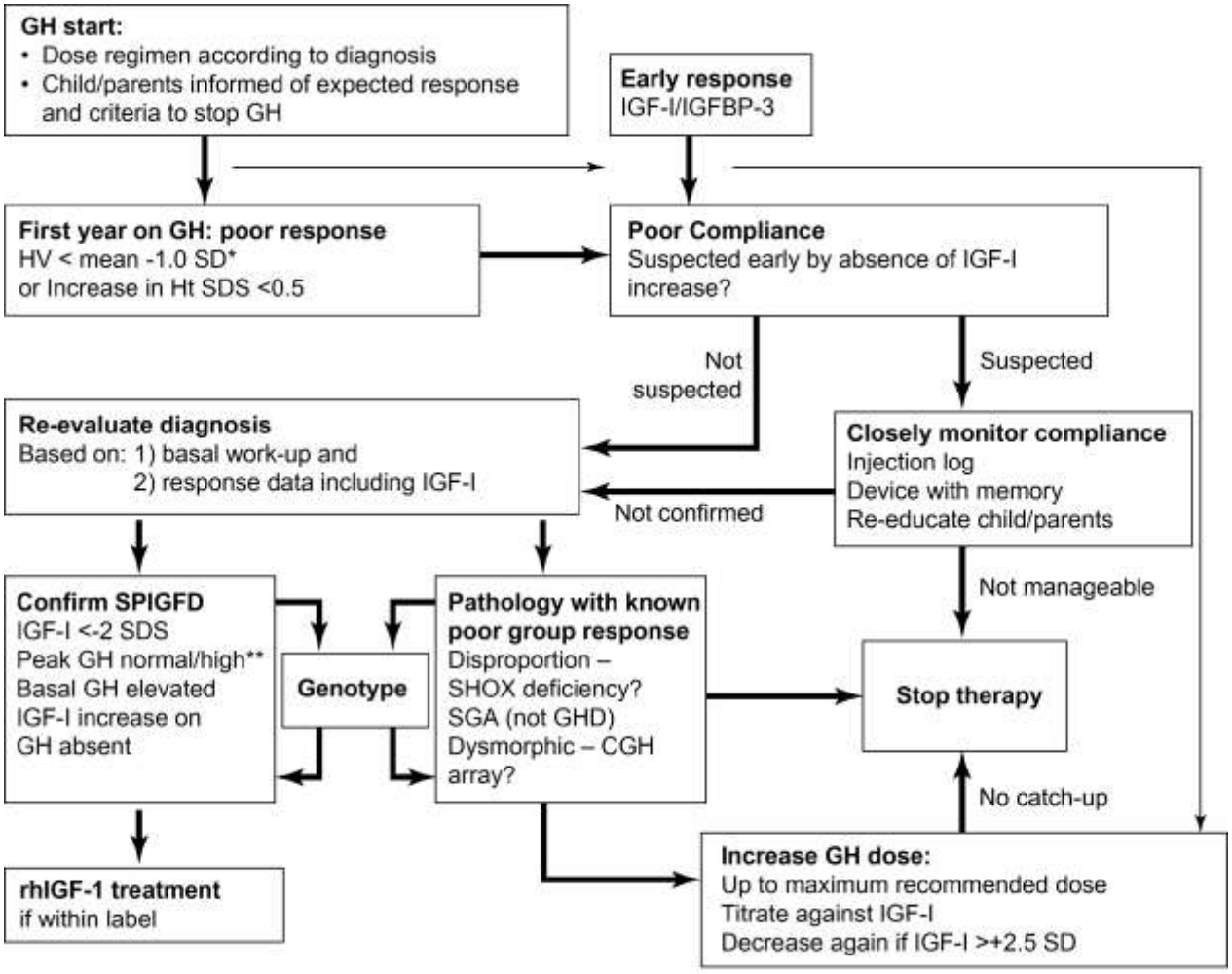

Fig. 5 –Algorithm for management of poor response to GH. *Height Velocity (HV) < mean −1.0 SD equals an increase in Ht SDS of 0.4 for severe IGHD and 0.3 for other diagnoses. Use reference for severe IGHD according to Ranke[10] for any diagnosis or if other diagnosis-specific references are used then consider using a more strict cut-off. ** Consider that GH stimulation tests were falsely low which is the case in the majority of 'IGHD' patients without MRI abnormalities. CGH array, comparative genomic hybridization array; SHOX deficiency, short stature homeobox-containing deficiency, SDS, standard deviation score; SGA, small for gestational age; SPIGFD; severe primary IGF deficiency.

Conclusions

The range of growth disorders treated with growth-promoting therapy includes a large number of disorders which vary in their phenotypic, biochemical and molecular characteristics. Consequently, variability of inherent responsiveness and responses in terms of short- and long-term change in height following treatment with GH or rhIGF-1 is to be expected. Some components of this variability can now be predicted and, therefore, prevented

by individualization of therapy. However, the reasons for others remain obscure and it has to be accepted that not all growth disorders are amenable to effective therapeutic management. Recognition of poor or suboptimal response, however, will contribute to the more effective management of short stature together with an awareness of the most appropriate therapeutic strategies and their implementation.

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Table 1

***Responses to GH therapy in children with diagnoses in the continuum of growth disorders*.**

Reference	Diagnostic groups (number of subjects)	Ht at start (SDS)	Age at start (yrs)	MPH (SDS)	Mean GH dose (µg/kg/day)	1st yr HV (SD) (cm/yr)	1st yr: gain in Ht (SDS)	First 2 yr Ht response Δ Ht SDS/ HV	Other measurements	Final height (SDS)	Comments
Bakker et al., 2008[3]	IGHD		8.0*		43	10.0 (1.3)					
	(n=3160)										
	OGHD		8.0*		42	9.9 (1.5)					
	(n=961)										
	ISS		8.0*		43	9.4 (1.0)					May include
	(n=1845)										SGA
	TS		8.0*		50	8.0 (0.7)					
	(n=1367)										
Ranke et al., 2010[10]	GHD (<5 µg/l)		7.2		33	10.0 (3.0)	1.04 (0.68)				
	(n=2863)		8.0*			9.2 (2.5)					
	GHD (5–10 µg/l)		7.8		32	8.4 (2.1)	0.72 (0.42)				

	(n=4663)		8.0*			7.9 (1.6)			
	TS		8.5		43	7.8 (1.8)	0.66 (0.38)		
	(n=3286)		8.0*			7.8 (1.6)			
	SGA		6.9		44	8.6 (1.9)	0.79 (0.45)		GH testing
	(n=1219)		8.0*			8.2 (1.3)			not required
Bang et al., 2011[4]	IGHD (<10 µg/l)	−3.2	6.6	−1.0	30	9.2 (2.0)	0.77 (0.46)	28 % with 1st yr Δ Ht	
	(n=173)**	(0.6)	(2.8)	(1.0)				SDS <0.5	
	OGHD	−3.2	5.5	−0.7	29	11.1 (4.7)	1.0 (0.8)	28% with 1st yr Δ Ht	
	(n=40)	(0.6)	(3.8)	(0.9)				SDS <0.5	
	SGA	−3.4	7.5	−1.2	33	8.0 (1.4)	0.52 (0.34)	46% with 1st yr Δ Ht	GHD
	(n=54)	(0.7)	(2.5)	(0.8)				SDS <0.5	excluded
	ISS	−3.2	7.3	−1.2	32	8.6 (1.4)	0.61 (0.30)	32% with 1st yr Δ Ht	SGA
	(n=37)	(0.5)	(2.4)	(0.8)				SDS <0.5	excluded
	TS	−3.0	7.7	−0.5	36	8.0 (1.5)	0.51 (0.27)	56% with 1st yr Δ Ht	
	(n=43)	(0.7)	(3.4)	(0.9)				SDS <0.5	
Ranke et al., 1999[9]	IGHD	−2.6	7.3	−0.6	43	9.2 (2.3)			
	(n=593)	(0.8)	(2.4)	(1.0)					
Kriström et al., 1997[29]	IGHD, ISS, SGA	−2.7	8.9	−0.9			0.80 (0.34)		
	(n=193)	(0.7)	(2.8)	(0.8)					

Jorge et al., 2006[30]	Severe GHD	−4.3	9.3	−0.86	33	10.6 (2.3)	0.9 (0.5)			−0.8 (1.1)	*GHR* fl/fl
	(n=75)	(1.1)	(3.5)	(0.75)							
		−4.2	8.5	−0.98		12.3 (2.6)	1.4 (0.6)			−1. 7 (1.2)	*GHR* fl/d3 or
		(1.8)	(4.1)	(0.94)							d3/d3
Rachmiel et al., 2007[31]	GHD (n=96)	−2.87	11.9	−0.49	26	9.0 (2.4)			Gain Ht SDS start-FH:	−1.04 (1.00)	
			(4.5)	(0.82)					1.8 (1.2)		
Leschek et al., 2004[32]	ISS	−2.7	12.5		31				Δ Ht SDS 0.57	−1.77 ± 0.17	
	(GH, n=37;								(3.7 cm >controls)	SDS, (−2.34 ±	
	control, n=31)									0.17 SDS in	
										control)	
Dahlgren et al., 2007[23]	IGHD + SGA +	−2.87	8.72		37		0.75 (0.3)	1.18 (0.44)			
	ISS	(0.6)	(2.41)								
	(n=415)										
Dahlgren et al., 2005[33]	SGA (n=77)	−2.8	10.7	−1.2					Δ Ht SDS start–FH:	−1.2 (0.7)	>2 yr pre-pub
		(0.7)	(2.5)	(0.9)					1.2 if not GHD		
									1.9 if GHD		
									0.8 if not GHD	−1.6 (0.8)	<2 yr pre-pub
									1.6 if GHD		
Ranke et al., 2007[24]	ISS (n=657)	−2.5	7.8	−1.4	27	7.9	0.52		Δ Ht SDS start–FH:		
			(4.7–	(−2.6–		(6.3–10.1)	(0.26–0.94)		1.1		

			10.6)	0.1)							
	Near FH group	−2.5	10.0	−1.0							
	(n=256)		(6.6–	(−2.6–							
			12.8)	0.4)							
Albertsson–Wikland et	ISS (n=108)	−2.75	11.3	−1.27	33			Δ Ht SDS start–FH: 1.3	−1.5	−1.7	Includes SGA
al., 2008[26]		(0.54)	(1.4)	(0.88)				(0.78) in 5.9 (1.1) years	(0.8)		
					67				@	−1.4	
Kriström et al., 2009[5]	GHD				40§§		1.31 (0.47)§§§				
	(n=110)	−2.72§	7.3§	−0.98§							
	ISS	(0.46)	(2.06)	(0.65)	50§§		1.36 (0.47)§§§				
	(n=43)										
Cohen et al., 2007[34]	GHD	−2.64	7.53		41 (34–45)	9.01	1.0/8.16				(conventional
	(~ 50%)	(0.61)	(2.40)								dosing)
	and ISS				28 (9–114)	9.71	1.08/8.38				(titrated to
	(~ 50%)										IGF-I 0 SDS)
	(n=147)				98 (20–346)	11.20	1.58/10.03				(titrated to
											IGF-I +2
											SDS)

*read-out from on GH HV curves at 8 years or from table provided in Ranke et al.[10]

**1st year height velocity, cm/yr (SD) = IGHD <3 µg/l (n=21): 11.2 (2.5); IGHD 3–7 µg/l (n=121): 9.0 (1.9); IGHD >7 µg/l (n=31): 8.6 (1.2)

@ −2.4 (0.85) final height in non-Tx controls

§ Figures are for individualized dosing group.

§§ In the standard dose group GHD and ISS children *received* 43 µg/kg/day

§§§ Mean gain in height SDS was 1.32 in individualized-dose and fixed dose groups.

Ht SDS, height standard deviation score; MPH, mean parental height; HV, height velocity; IGHD, idiopathic growth hormone deficiency; OGHD, organic growth hormone deficiency; ISS, idiopathic short stature; SGA, small for gestational age; TS, Turner's syndrome; *GHR* fl, full length *growth hormone receptor (GHR)* genotype; *GHR* d3, exon-3 deleted *GHR* genotype; FH, final height; pre-pub, pre-pubertal; Tx, treated; FSS, familial short stature;