# DIAGNOSIS AND MANAGEMENT OF GROWTH DISORDERS IN GULF COOPERATION COUNCIL (GCC) COUNTRIES: CURRENT PROCEDURES AND KEY RECOMMENDATIONS FOR BEST PRACTICE

# Growth hormone therapy

# Factors influencing individualization of hGH therapy

# Recommendations



- Growth hormone deficiency in children covers a wide range of GH secretory abnormalities, ranging from extreme deficiency in congenital hypopituitarism to mild or partial deficiency, which normalizes during exposure to sex steroids in puberty.

- It is clear from the model that patients with severe GH deficiency have greater sensitivity and responsiveness to hGH therapy than patients with mild or partial deficiency.
- This variation in responsiveness is demonstrated in clinical practice, whereseverely GH-deficient subjects (peak GH <3 mg/L) have superior growth responses compared to milder cases (peak GH 3e10 mg/L) and is also a key finding in analysis of data used to construct mathematical growth prediction models.

- The variation in GH responsiveness is even more marked when non-GH deficiency disorders such as Turner syndrome and short stature secondary to SGA are treated with hGH.
- When GH-deficient patients are treated with a fixed dose of GH calculated for body weight or surface area, the mean response and stature at adult height may appear satisfactory, but a considerable variation in responses exists.

- This variation is reduced when the hGH dose is individualized for each patient, depending on the variables predicting the likely response.
- The key variables are:
- > diagnosis of the growth disorder,
- > age at start of therapy,
- >peak GH during a GH stimulation test in GH deficiency,
- >height SDS compared with mid-parental height SDS,
- >dose of hGH.
- When hGH therapy is initiated, all of these factors should be taken into consideration to calculate the dose.

# Responses to hGH therapy in GH deficiency

# Recommendations



- Evidence-based data supporting the key factors predicting growth response during the first and second years of hGH therapy in GH deficiency should be considered when the starting dose of hGH is selected.
- Key predicting factors are:
- > severity of GH deficiency,
- > age of the patient,
- > distance between the patient's height SDS and mid-parental height SDS.

- Subjects with multiple pituitary hormone deficiencies experience better growth than individuals with isolated GH deficiency.
- The starting dose of hGH should follow EMA and US Pediatric Endocrine Society guidelines of 23-39 mg/kg/day, i.e., 0.18-0.25 mg/kg/week.

- Patients with severe GH deficiency, i.e., peak GH <3 mg/L, and patients with multiple anterior pituitary hormone deficiencies require hGH doses at the lower end of the recommended range, whereas patients with mild or partial GH deficiency require doses at the upper end of the range.
- The increase of hGH dose during puberty is not recommended.

- Following the initiation of hGH therapy, there is a need to define a poor or unsatisfactory response and to prevent or correct it by optimizing treatment within accepted guidelines.
- Poor responses to hGH are relatively common, and recognition of a poor response is an indication for action, either to modify the therapy or to review the primary diagnosis.

- Unfortunately, no international consensus exists on the definition of a poor first-year growth response.
- Bakker et al suggested that GH-deficient patients with a first-year height velocity less than a mean HV 1.0 SD for that sex and diagnosis should be labeled as poor responders.
- Similarly, Ranke argued that a poor response equals a gain in height SDS of <0.4 in a patient with severe GH deficiency and an increase in height SDS of <0.3 in patients with less severe GH deficiency, girls with TS or SGA subjects.

- A change in height SDS >0.5 during the first year of therapy generally indicates that the patient is experiencing catch-up growth.
- In contrast, a change in height SDS <0.3 indicates a poor response.

- Measurement of IGF-1 concentration is recommended for children with GH deficiency treated with hGH, with the aim of normalizing serum IGF-1 concentrations.
- However, evidence is lacking that supports the value of IGF-1 monitoring for safety in children and the lack of any data to indicate a safe upper limit for serum IGF-1 concentrations.

# Responses to hGH therapy in Turner syndrome, short stature related to SGA and idiopathic short stature

# Recommendations

# Turner syndrome



- The beneficial pharmacological effect of hGH therapy on growth in Turner syndrome patients is now established, and a general agreement exists that the hGH dose of choice should be approximately 50 mg/kg/day.
- Key factors predicting the growth response to hGH are:
- > the dose of hGH,
- > a young age at initiation,
- > the duration of therapy

- Children started on hGH before the age of four years are particularly responsive.
- A small additional gain in adult height (2.3-4.6 cm) has been reported if the mild androgen oxandrolone (0.03-0.05 mg/kg/day) is given starting at 8-10 years of age in addition to hGH.

- Debate remains concerning the optimal regimen for estrogen replacement in girls or adolescents with Turner syndrome.
- Quigley et al have recently presented compelling results showing advantages in terms of growth, pubertal development, and cognitive function when very low-dose estrogen replacement was commenced from the age of five years.

- Whether a regimen such as this or estrogen commencement at the physiological age of puberty is chosen, agreement exists that delaying sex steroid replacement until the mid-teen years, with the aim of prolonging and improving hGH-induced height gain, is disadvantageous for the patient.

# Small for gestational age



- The criteria for hGH therapy in SGA subjects differ between the FDA and EMA approval guidelines.
- However, there is agreement that hGH can induce significant gain in adult height.
- Research data has demonstrated rapid height gain in young, pre-school SGA subjects treated with hGH, and early diagnosis and initiation of therapy is strongly recommended.

- Catch-up growth occurs more rapidly when an hGH dose of approximately 67 mg/kg/day is used and maintained for up to four years.
- However, the dose of hGH recommended in the EMA license is 35 mg/kg/day, which also induced significant adult height gain.

- This was further increased marginally by the addition of a GnRH analogue to suppress puberty.
- Convincing evidence is available suggesting that a delay in hGH treatment until less than two years before the physiological onset of puberty compromises adult height gain.

# Idiopathic short stature



- In 2003, the FDA approved ISS as a licensed indication for hGH therapy for patients with height 2.25 SD and a reduced adult height expectation.
- No agreement exists on the optimal therapeutic approach to such patients; however, because these patients do not have GH deficiency, a pharmacological dose of approximately 50 mg/kg/day has been recommended.

- In a recent Nordic study , no difference was observed in the first-year growth response to
- hGH in patients with mild GH deficiency (peak GH 3-7 mg/L) and with ISS (peak GH >7 mg/L).
- Age at the start of therapy and dose of hGH are the two key factors predicting growth response.

- However, as the quality of response in ISS is unpredictable, and the rate of poor response is 30%- 40% , an approach to the family explaining this information is important.
- The first-year response will correlate with long-term benefits; therefore, assessment of change in height SDS at the end of the first year of hGH therapy is essential.

- In patients who show a change of height <0.3 SDS, discontinuation of treatment is recommended.
- Some slight additional gain in pubertal growth may be achieved by the addition of a GnRH analogue to hGH.
- In this case, the analogue should be commenced in early puberty and continued for a minimum of two years.

Table 4 Recommended approach and hGH treatment regimens for patients with Turner syndrome, SGA and idiopathic short stature (ISS).

| | Turner syndrome | SGA (birth weight/length ≤ −2 SD) | ISS |
|---|---|---|---|
| Factors predicting response [55] | • hGH dose<br>• Age<br>• Weight SDS<br>• Oxandrolone | • hGH dose<br>• Age<br>• Weight SDS<br>• MPH SDS | • Age<br>• hGH dose<br>• Weight SDS<br>• Height − MPH SDS |
| hGH dose (μg/kg/day) | 50 | 35[a]<br>67[b] | 50 |
| Starting height (SDS) | – | −2.5[a]<br>−2.5[b] | −2.25[b] |
| Starting age (years) | – | 4[a]<br>2[b] | – |
| Key comments | • Early diagnosis<br>• Oxandrolone <0.06 mg/kg from 8 to 10 yr<br>• Sex steroids at physiological age<br>• Transition essential | • Early diagnosis<br>• Increased catch-up with higher hGH dose<br>• Start hGH >2 yr before puberty | • Response unpredictable<br>• If no response (Δ height SDS <0.5) after year 1, stop hGH |

# Adherence to hGH therapy: prevention and management of poor adherence

**Table 6** The most common reasons for poor adherence to hGH therapy.

- The child's and care-giver's lack of understanding of the primary disease
- Adolescence
- The length of treatment anticipated
- Implications of poor adherence regarding growth response
- Inadequate support and monitoring by healthcare providers including inconsistent contact
- Pain and discomfort of injections
- Fear of needles
- Lack of choice of injection device and/or complicated devices
- Parental lifestyles and inadequacy of support of the child
- Inconvenience of injection schedule
- Dissatisfaction with the growth response

# GROWTH HORMONE THERAPY IN CHILDREN; RESEARCH AND PRACTICE – A REVIEW

# Initial rhGH-management and monitoring of rhGH therapy

# GH dose adjustment and monitoring



- The most common method of adjusting rhGH dose in order to obtain and maintain the expected growth velocity is based on body weight and growth velocity, although body surface area is also used.
- Prediction models are available to calculate the initial dose based on diagnosis and goal as well as to follow the adequacy of dose/response.

- An insufficient response may indicate the presence of associated conditions preventing the expected growth response or inadequate compliance to treatment, but may also suggest that the initial diagnosis is not correct; it may even suggest that there is a reason to re-evaluate the benefits of the treatment.

- The initial studies that led to the approval of rhGH used growth velocity and change in weight to adjust rhGH dosage.
- In 2007, Cohen *et al demonstrated that IGF-I levels could be used to adjust rhGH dosage* in children with GHD and ISS.
- They demonstrated that maintaining the IGF-1 level close to the mean for age and gender elicited a similar 2 year growth response compared with methods of rhGH dosage based on weight, but using a lower mean dose of rhGH and avoiding supraphysiological serum levels of IGF-I, suggesting that this strategy could improve safety as population studies demonstrated a correlation between higher IGF-I and some cancers in the normal adult population.

- On the other hand, in conditions associated with mild GH and/or IGF-I resistance, higher rhGH doses and/or IGF-I serum levels to achieve the expected clinical response may be necessary.
- There are no data demonstrating that above normal levels of IGF-I during rhGH therapy causes any harm.

- There are two other aspects to consider when treating children with rhGH:
- (1) different individuals may have different sensitivity to GH and to IGF-I and the sensitivity in different tissues in the same individual may also differ, with higher doses of GH and levels of IGF-I causing different local effects in each person and
- (2) IGF-I circulates in serum bound to IGFBPs and ALS.

- Some population studies demonstrated that higher serum IGFBP-3 is associated with a lower incidence of malignancies.
- It has been suggested that free IGF-I index or IGF-I/ IGFBP-3 be used as a safety measure, although there are no data to support such practice.

- On the other hand, some non-GHD children may require supraphysiologic levels of IGF-I to obtain the desired beneficial aspects of treatment.
- Since there are inadequate data available to indicate a safe upper limit for serum IGF-I concentrations and the safety implications of higher serum IGF-I levels are unknown, if an adequate growth velocity is obtained with normal levels of IGF-I in these children, supraphysiological levels may not need to be maintained.

# Care with unmasking other conditions

# Cortisol deficiency



- GH inhibits 11β-hydroxysteroid dehydrogenase type 1, which is responsible for the conversion of cortisone (inactive) into cortisol (active).
- Initiation of rhGH therapy in patients with subclinical adrenocorticotropic hormone (ACTH) deficiency may induce symptomatic adrenal insufficiency requiring glucocorticoid replacement.
- Patients already on cortisol replacement may need an upward dose adjustment.
- Caretakers should look for symptoms of adrenal insufficiency after starting GH in patients at risk for ACTH deficiency.

# *Hypothyroidism*



- GH increases the peripheral conversion of thyroxine (T4) to tri-iodothyronine.
- Commencing GH replacement may therefore unmask preexisting central hypothyroidism as defined by a fall of serum-free T4 into the subnormal range.
- Thyroid function should be monitored and adjustment of the T4 dose may be needed after initiation of rhGH.

# *Diabetes Mellitus*



- GH increases insulin resistance but it is not associated with the development of diabetes mellitus, although the addition of rhGH in children with impaired insulin secretion/action, may cause enough insulin resistance leading to the appearance of hyperglycemia.
- Hemoglobin A1C and glucose should be monitored in patients at risk for developing diabetes mellitus.

# Management of the poorly growing child on growth hormone

- Treatment with rhGH at the currently used doses increases adult height in most children with short stature.
- There are two main groups of children who grow poorly on rhGH:
- 1)those who did not increase height velocity when starting treatment
- 2)those who had an increment in the growth velocity but subsequently changed to a sub-normal height velocity.

- Because there is a continuum of GH responses, the definition of nonresponsiveness is arbitrary.
- Suggested criteria for poor first year response include height velocity SDS less than −1 or change in height SDS<0.3–0.5, depending on age.

# *Children who did not increase HV upon starting treatment with rhGH*



- The main reasons for a child not to have an increment in growth velocity when starting rhGH are:
- (1) lack of adequate storage of the rhGH,
- (2) lack of understanding of the methods of administration of medication or non-compliance,
- (3) inaccurate diagnosis,
- (4) unrealistically high growth expectations.

- If the initial response is considered inadequate, the approach is to review with patient and family the understanding of treatment and techniques of administration of the medication.
- If those are appropriate, changes in serum IGF-I when comparing pre and post treatment may help.

- If pretreatment serum IGFI levels were higher than expected, the initial diagnosis should be questioned.
- If there was no change in IGF-I, GH insensitivity, conditions that affect growth and IGF-I synthesis (inflammatory bowel disease for example) and adherence issues should be further investigated.

# *Children with a normal initial response but subsequent decreased height velocity*



- The main reasons for a decrement in growth velocity while on rhGH are:
- (1) lack of adequate compliance/adherence,
- (2) development of antibodies to GH,
- (3) development of a secondary condition that affects growth (hypothyroidism, enteropathies – inflammatory bowel disease or celiac disease, Cushing's disease, other chronic illnesses/malnutrition),
- (4) lack of sex steroid exposure at the appropriate ages,
- (5) closure of growth plate.

- When there was an initial response followed by a low height velocity, lack of compliance is the most common cause.
- In patients with isolated GHD, the development of anti-GH antibodies should be investigated in those with type 1a GHD.

- Investigating other secondary causes for failure to grow can initially be oriented based on risks specifics for each group.
- For example, girls with Turner syndrome have a higher chance of developing primary hypothyroidism.
- Patients with abnormal pituitary anatomy or post cranial radiation may develop central hypothyroidism.
- In children with peripubertal age, the lack of sex steroids may affect height velocity.

# TOWARDS OPTIMAL TREATMENT WITH GROWTH HORMONE IN SHORT CHILDREN AND ADOLESCENTS: EVIDENCE AND THESES

# How to Evaluate the Response to GH

- whether or not the magnitude of a response parameter reflects an ‘adequate’ growth response cannot be concluded from its face value.
- Since there is no known quantitative measure of an objectively adequate response to a dose of GH in an individual with a specific diagnosis, the interpretation of the observed response variable must be evaluated by comparison with references empirically derived from other comparable (i.e. equally defined diagnostic entity) individuals treated with GH.

- For such a purpose, two separate approaches have been pursued:
- (1) establishing empirical growth references
- (2) developing prediction models for the growth response.

# GH doses recommended for different indications

| Indication | Europe (EMA) µg/kg/day | Japan (PMDA) mg/kg/week | USA (FDA)[1] | |
|---|---|---|---|---|
| | | | mg/kg/week | µg/kg/day |
| GHD | 25–35[2] | 0.175 | 0.16–0.30[2] | 23–43 |
| PWS | 35 | 0.245 | 0.24 | 34 |
| TS | 45–50 | 0.35 | 0.33–0.47 | 47–67 |
| CRI | 45–50 | 0.175–0.35 | 0.35 | 50 |
| SGA | 35 | 0.23–0.47 | 0.47–0.48 | 67–69 |
| SHOX haploinsufficiency | 50 | not approved | 0.35 | 50 |
| ISS | not approved | not approved | 0.30–0.47 | 43–67 |
| NS | not approved | not approved | up to 0.46 | up to 66 |

# Pretreatment strategy

| | |
|---|---|
| Diagnostic path | clinical, anthropometrical, radiological, and biochemical work-up with standardized methods; in suspected disorders of the GH-IGF axis, but uncertain test results, repeat investigations; establish causality of growth disorder |
| GH status of diagnosis | GHD disorder vs. non-GHD disorder |
| Approval of GH | GH approved vs. GH not approved |
| Outcomes, spontaneous | estimate of spontaneous adult height without GH treatment/replacement |
| Outcomes, with GH | estimate potential of individual adult height/gain in height (long-term prediction) |
| Risk assessment | attempt an estimate of individual risk of GH treatment; investigate disease-specific risk factors; action plan in case of side effects |
| Treatment decision | follow-up plan (see below) |
| GH brand | choose GH formulation and injection device |
| GH dose | choose starting GH dose (within approved dose range) |
| Estimate 1st-year growth | predict 1st-year growth response; action plan for deviation from expected growth; discuss exit scenario with patient |

# Intervals of Follow-Up

# First year on GH and prepubertal follow-up strategy

| | |
|---|---|
| At start | assure that all parameters required for establishing diagnosis and risks of treatment and for follow-up are documented (preserved) |
| First weeks on GH | assure injections of GH during initial week; measure biochemical parameters of response and adherence thereafter (e.g. IGF-I and 'IGF-I generation test') |
| First year on GH | follow-up at 3, 6, (9), and 12 months [clinical and biochemical parameters of response/adherence (e.g. IGF-I)]; if not indicated, do not change GH dose during first year |
| After 12 months on GH | calculate HV (cm/year) and/or ΔHt SDS (CA); if references are available: (1) compare response with empirical growth references and (2) calculate responsiveness – index of responsiveness (IoR) – with prediction model |
| Disease-specific empirical references [79, 80] | disease-specific references available (response):<br>a 'normal' growth = –1.0 to +1.0 SDS or 25th to 75th centile<br>b 'poor' growth = <–1.0 SDS or <25th centile<br>c 'good' growth = >+1.0 SDS or >75th centile<br>disease-specific references (non-GHD) not available:<br>use SGA references as an estimate |

| | |
|---|---|
| Prediction models | prediction models available; calculate index of responsiveness (IoR):<br>a 'normal' IoR = –1.0 to +1.0 SDS or 25th to 75th centile<br>b 'poor' IoR = <–1.0 SDS or <25th centile<br>c 'good' IoR = >+1.0 SDS or >75th centile |
| Adult height prediction | calculate predicted adult height based on observed 1st-year IoR:<br>a if adult height prognosis normal and IGF-I SDS levels within upper norm (>0.0 <+2.0 SDS), continue with same dose<br>b if adult height prognosis poor (<–2.0 SDS) and IGF-I SDS levels low (<0.0 SDS), increase GH dose (up to approved limits) |

Considerations according to response and IoR

a response and responsiveness (IoR): 'poor':
ΔIGF-I on GH <0.5 SDS
consider GH resistance, if adherence assured
consider end of GH treatment

b IGF-I on GH >1.0 SDS
consider IGF resistance
consider ending GH treatment

response 'normal' and responsiveness (IoR) poor:
reconsider diagnosis

response 'poor' and responsiveness (IoR) normal:
consider increasing GH dose

response and responsiveness (IoR): good:

a IGF-I SDS levels >+2.0 SDS: reduce GH dose by 20%, follow IGF within 1–3 months

b IGF-I SDS levels normal and adult height prognosis good: consider reducing GH dose by 20%, follow IGF-I within 1–3 months

# At puberty onset

| | |
|---|---|
| Puberty onset | if spontaneous pubertal onset precocious, treat accordingly<br>if spontaneous pubertal onset delayed, consider induction of puberty |
| Expected adult height | Calculate expected total pubertal growth based on prediction models (if available) or prediction systems based on bone age<br>a if expected adult height within the normal range:<br>continue prepubertal GH dose<br>b if expected adult height below normal range:<br>estimate further gain of height by increasing to pubertal GH dose<br>if normalization of adult height not likely by pubertal GH dose, consider additional medication to delay puberty |