Growth Hormone Research Society perspective on biomarkers of GH action in children and adults.

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Growth Hormone Research Society perspective on biomarkers of GH action in children and adults

Gudmundur Johannsson1, Martin Bidlingmaier2, Beverly M K Biller1, Margaret Boguszewski6, Felipe F Casanueva5, Philippe Chanson4, Peter E Clayton7, Catherine S Choong8, David Clemmons2, Mehul Dattani15, Jan Frystyk1, Ken Ho12, Andrew R Hoffman13, Reiko Horikawa18, Anders Juul15, John J Kopchick16, Xiaoping Luo17, Sebastian Neggers18, Irene Netchine19, Daniel S Olsson20, Sally Radovick21, Ron Rosenfeld22, Richard J Ross23, Katharina Schilbach5, Paolo Solberg24, Christian Strasburger25, Peter Trainer26, Kevin C J Yuen27, Kerstin Wickstrom28 and Jens O L Jorgensen29 on behalf of the Growth Hormone Research Society

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Abstract


Participants: GRS invited 34 international experts including clinicians, basic scientists, a regulatory scientist and physicians from the pharmaceutical industry.

Key Words

- GH
- IGF-I
- GH deficiency
- acromegaly
Evidence: Current literature was reviewed and expert opinion was utilized to establish the state of the art and identify current gaps and unmet needs.

Consensus process: Following plenary presentations, breakout groups discussed questions framed by the planning committee. The attendees re-convened after each breakout session to share the group reports. A writing team compiled the breakout session reports into a document that was subsequently discussed and revised by participants. This was edited further and circulated for final review after the meeting. Participants from pharmaceutical companies were not part of the writing process.

Conclusions: The clinical endpoint in paediatric GH treatment is adult height with height velocity as a surrogate endpoint. Increased life expectancy is the ideal but unfeasible clinical endpoint of GH treatment in adult GH-deficient patients (GHDA) and in patients with acromegaly. The pragmatic clinical endpoints in GHDA include normalization of body composition and quality of life, whereas symptom relief and reversal of comorbidities are used in acromegaly. Serum IGF-I is widely used as a biomarker, even though it correlates weakly with clinical endpoints in GH treatment, whereas in acromegaly, normalization of IGF-I may be related to improvement in mortality. There is an unmet need for novel biomarkers that capture the pleiotropic actions of GH in relation to GH treatment and in patients with acromegaly.

Introduction

Biological markers (biomarkers) play an essential role in the clinical care of patients, drug development and regulatory approval. Furthermore, biomarkers are linked to surrogate endpoints and clinical endpoints (1, 2, 3, 4). The requirement for rigorous procedures utilizing biomarkers in drug development is evident and recognized (2, 5). The obvious biomarkers of growth hormone (GH) action in children and adults are serum levels of GH itself and of insulin-like growth factor-I (IGF-I). Both are used diagnostically; IGF-I is used to monitor the effects of GH replacement in GH deficiency (GHD), and both GH and IGF-I are used in the diagnosis and management of acromegaly. While serum IGF-I level is used as a surrogate endpoint in trials involving GH treatment and medical treatment of acromegaly, neither GH nor IGF-I has been subject to a structured evaluation as biomarkers, nor do we have a comprehensive definition of clinical endpoints for the treatment of GH-related disorders. Therefore, there is a need to define clinically relevant endpoints and identify and evaluate current and novel surrogate endpoints and biomarkers of therapies targeting GH.

The Growth Hormone Research Society (GRS) convened a Workshop in Aarhus, Denmark, on November 15–18, 2017 to review the current state of the field and address key issues regarding the definition of clinical endpoints for GH therapy and treatment of acromegaly, to critically evaluate current surrogate endpoints for GH therapy and treatment of acromegaly and to discuss novel and potential biomarkers of GH action in children and adults.

Methods

The structure of this Workshop was adapted from prior Workshops organized by GRS (6, 7, 8). Thirty-four invited international leaders from twelve countries across five continents participated. These included paediatric and adult endocrinologists, basic scientists, a European medicines regulator and physicians from the pharmaceutical industry. A review of the current status of clinical endpoints and biomarkers was written prior to the meeting. A planning committee of the GRS comprised academic adult and paediatric endocrinologists who determined the agenda, selected speakers to summarize key relevant topics and formulated the questions for discussion.

Following presentations that summarized the literature, three breakout groups addressed each topic in more detail by discussing the list of questions formulated by the planning committee and subsequently agreed upon by all participants. All attendees re-convened after each of the breakout sessions to share reports from the groups. At the end of days 1 and 2, a writing team compiled the breakout group reports into a final document that
was discussed and reviewed in its entirety and revised by participants on the concluding day. When there was no clear agreement by most participants, consensus was reached by voting. This draft document was edited further for formatting and references, and subsequently circulated to the academic attendees for final review after the meeting. Meeting participants from pharmaceutical companies, who participated in the Workshop, were not part of the writing team and were not present during text revision on the final day, but they were shown the manuscript before submission to identify factual errors. This report is a concise chronicle of the Workshop and is not intended to be an exhaustive review of the literature on this topic. It was written utilizing: (1) the content from the speaker presentations and the current literature in the field, (2) the combined comments of the breakout groups to the questions and (3) the collective remarks of the entire group during report-back sessions.

Definitions

The following terms and definitions, which derive from an NIH expert working group (1) were used in the Workshop:

Clinical endpoint: A characteristic or variable that reflects how a patient feels, functions or survives.

Biomarker: A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention.

Surrogate endpoint: A biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence.

A major emphasis was made on measures of treatment efficacy and safety.

Clinical and surrogate endpoints during GH treatment

Paediatric GH therapy

Adult height is the ultimate clinical endpoint of GH therapy in children (9), although it is recognized that normalization of height during childhood, independent of eventual height, is an additional goal. A uniform definition of adult height in the context of GH therapy in children is not available, but a pragmatic definition used in several trials have been a height gain <2 cm over the last 12 months. In clinical practice and in clinical trials, change in height velocity (cm/year) or change in height standard deviation score (SDS) are used as surrogate endpoints of efficacy and to monitor adherence to therapy in individual children with GHD (Table 1). In children being treated with GH for non-GHD conditions, the change in height velocity or height SDS is used as surrogate endpoints. In patients with Prader–Willi syndrome, although auxological measures are important, measures of the metabolic actions of GH are also valuable, including change in body mass index (BMI) and body composition (10). This also applies to other conditions such as children born small for gestational age. Growth response during the first year of GH treatment for short

<table>
<thead>
<tr>
<th>Patients and treatments</th>
<th>Clinical efficacy endpoints</th>
<th>Surrogate endpoints</th>
<th>Biochemical biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric GH treatment</td>
<td>Adult height</td>
<td>Change in height SDS/growth velocity</td>
<td>IGF-I</td>
</tr>
<tr>
<td>GH deficiency</td>
<td>Body composition</td>
<td>Peak bone mass, DXA Z score, LBM, and FM</td>
<td>IGF-I</td>
</tr>
<tr>
<td>GH deficiency in the transition period</td>
<td>Adult height</td>
<td>Change in height SDS/growth velocity</td>
<td>IGF-I</td>
</tr>
<tr>
<td>Adult height treatment</td>
<td>Adult height</td>
<td>Muscle tone</td>
<td>IGF-I</td>
</tr>
<tr>
<td></td>
<td>Body composition</td>
<td>Anthropometry, DXA Z score, LBM and FM</td>
<td>IGF-I</td>
</tr>
<tr>
<td>Acromegaly treatment</td>
<td>Serum IGF-I and GH reduction</td>
<td>Symptom relief</td>
<td>IGF-I</td>
</tr>
</tbody>
</table>

CRI, chronic renal insufficiency; DXA, dual X-ray absorptiometry; FM, fat mass; IGF-I, insulin-like growth factor I; ISS, idiopathic short stature; LBM, lean body mass; SDS, standard deviation score; SGA, small for gestational age; SHOX, short stature homeobox deficiency; SRS, Silver–Russell syndrome.
stawture is correlated with growth rates in subsequent years and adult height. Prediction models using auxology, bone age and other variables have been advocated as tools for individual patient management (10, 11, 12). Measurement of body proportions can be helpful in certain subgroup of patients, such as cancer survivors receiving spinal radiation. Bone age and decrease in growth velocity can be used as biomarkers for epiphyseal maturation to determine the time at which GH treatment should cease.

**Transition from childhood to adult GH replacement therapy**

At the time when a patient reaches adult height, GHD is either reconfirmed by retesting or recognised as a lifelong condition based on the underlying pathology. Since growth can no longer be used as a biomarker, the clinical focus in patients during the transition turns to adult endpoints, such as peak bone mass and body composition including fat mass and lean body mass (13).

**Adult GH replacement**

Adult patients are only treated when there is an established diagnosis of GHD with the goal of replacing the insufficient hormone. Adult GHD is recognized as a syndrome with various and multifactorial comorbidities affecting different organ systems (14). Therefore, the impact of GH therapy cannot be directly correlated with a single clinical endpoint. Unlike in paediatric GH therapy, where measurement of growth is central to all GH-treated patients, the goals of adult GH replacement therapy take into consideration age, functional status and comorbidities.

Clinical endpoints for GH replacement in adults with GHD include body composition and quality of life (QoL). Measurement of body composition may include waist circumference, dual-energy X-ray absorptiometry (DXA) scan for bone mineral density and content (BMD/BMC), and where available, fat distribution such as truncal fat and lean body mass (Table 1). The routine consultation should include patient reported outcomes such as mood, motivation, energy levels, physical mobility, activities of daily living and employment. Formal questionnaires are used in some health systems to determine the eligibility for treatment and to monitor response to therapy (15).

A reduction in excess mortality in adult GHD would be an ideal clinical endpoint, but such data are unlikely to be forthcoming. The information available suggests there is an increased mortality in adult patients with hypopituitarism including GHD due to cardiovascular (CV) disease (16). Therefore, biomarkers for CV risk, including blood pressure, visceral fat, lipids and high-sensitive C-reactive protein (hsCRP), are commonly measured.

Safety is monitored by asking about GH side effects, including oedema, carpal tunnel syndrome and joint pains and via measurement of haemoglobin A1C (HbA1C) levels.

**Biochemical biomarkers during GH treatment**

**IGF-I**

Serum IGF-I is a biomarker of GH status, often being low in GHD and high in GH excess. It is not subject to the diurnal variation or pulsatility that is characteristic of endogenous GH secretion. GH has direct, IGF-I-independent actions as well as indirect effects mediated through hepatic and local tissue IGF-I production. Serum IGF-I, which mainly reflects liver-derived IGF-I, is suppressed during catabolic conditions and has significant within-individual and inter-assay variability (7, 17, 18). Despite these limitations, measurement of serum IGF-I levels is currently used as a biomarker for GH action (Table 1).

**Use of serum IGF-I in paediatric GH treatment**

Measurement of serum IGF-I during GH therapy in children is used as a biomarker for adherence. Its relationship to growth rate and final height is influenced by other variables including bone age, birth length and nutritional status, and it therefore has a limited role as a marker of efficacy. This is particularly true for subsets of non-GHD patients, who may have some degree of associated GH and IGF-I insensitivity (19). Failure to raise serum IGF-I concentrations during GH treatment may be an early indication of GH insensitivity and could warrant further evaluation and alternative treatments (20).

The increase in IGF-I with GH treatment is dose dependent and dosing can be adjusted with a goal of attaining an IGF-I within the normal range. However, as noted earlier, serum IGF-I has proved disappointing as a direct correlate to clinical outcome, but it is currently the best option available. This highlights the need for new biomarkers to predict the efficacy and safety of therapy in individual patients.

IGF-I is also used as a long-term safety marker during GH treatment. This practice is based on an extrapolation from epidemiologic data in healthy adult populations, and
meta-analyses and life course data in patients with acromegaly that have shown an increase in morbidity and mortality of subjects having upper-normal or consistently elevated IGF-I levels (6). Nevertheless, modestly and transiently elevated serum IGF-I concentrations in GH-treated paediatric patients have not been linked to adverse effects. There are no accepted guidelines for IGF-I levels during GH treatment in GHD children, but where possible, IGF-I should be maintained within the normal range, although modest elevations above +2 S.D. may be acceptable under certain circumstances. During the treatment of non-GHD states, in order to achieve an acceptable growth response, IGF-I may transiently be above the normal range; however, the safety implications are unknown.

**Use of serum IGF-I in transition and adult GHD**

During GH replacement, the GH dose in adults is titrated to target IGF-I levels within the normal range. Serum IGF-I levels do not correlate well with clinical endpoints, but may help guiding dose titration. Despite the limitations noted earlier, it is used as a biomarker for safety. GH dose during the transition period is typically in-between paediatric and adult doses, with adjustment primarily based on serum IGF-I, just as in adult patients (13).

**Insulin-like growth factor-binding protein 3 (IGFBP-3), acid-labile subunit (ALS) and bioactive IGF-I**

IGF-binding protein 3 (IGFBP-3) is the major carrier protein for IGF-I in serum. There are limited data indicating that IGFBP-3 predicts GH responsiveness or safety. However, epidemiologic data suggest that high IGFBP-3 levels may reduce the IGF-I-associated risk of certain cancers (21). Therefore, additional studies measuring IGF-I, IGFBP-3 and their molar ratio during GH therapy as safety markers may be useful. Bioactive IGF-I as measured by the kinase-receptor activation (KIRA) assay is a useful research tool and accurately reflects changes in GH-responsive proteins (22). However, this assay is labour-intensive and costly and at the current time cannot be utilized in large clinical studies or clinical practice. The ALS is a GH-dependent protein, but its usefulness in clinical practice has not been established (23).

**Biomarkers in the context of long-acting growth hormone (LAGH) products**

Neither daily GH administration nor LAGH recapitulate the natural pattern of GH secretion. Unlike daily GH, steady state IGF-I levels do not occur with LAGH products. Each of these novel products has a unique pharmacodynamic (PD) profile, which means that they cannot be considered as a homogenous group. Modelling approaches based on PD measurement can be used to indicate the optimal time for serum IGF-I measurement for dose titration purposes (24). The relationship between IGF-I and IGFBP-3 may also be different among the various LAGH products (25). Since some of these agents are GH analogues as opposed to authentic GH, they may potentially exert other biological effects that could affect safety and efficacy. This suggests there may be a need to develop biomarkers that are specific for a given LAGH product. Given the differences among these products, specific pharmacovigilance programmes may be essential for each LAGH product (8).
assessing the effect of pituitary surgery and is an index of completion of tumour removal. Clinical practice varies regarding the method used to evaluate GH; random measurements, oral glucose suppression of GH and ‘day curves’ with timed measurements across the day have all been used (30).

It can be difficult to determine whether treated patients with discordant IGF-I and GH levels are optimally controlled. There are a number of reasons for this discrepancy, such as oral oestrogen treatment, nutritional status, history of pituitary radiotherapy, assay variability and inadequate reference ranges. In addition, there are therapy-specific changes that can lead to this discrepancy. For example, during somatostatin analogue treatment, there is a reduction in serum IGF-I that is not associated with a proportional reduction of GH (31). Measurement of GH is not helpful during treatment with GH receptor antagonists (32). Consideration of these factors should be taken into account before making therapeutic decisions.

Measurement of serum IGFBP-3 or ALS does not provide additional value beyond serum IGF-I in the routine management of patients with acromegaly.

Treatment should be monitored according to the treatment-specific side effects. Monitoring of glucose metabolism and CV risk factors is standard of care for patients with acromegaly (33). Potent therapies for acromegaly may result in overtreatment, as manifested as subnormal levels of serum IGF-I.

Novel biomarkers – an unmet need

GH and IGF-I have been used as biomarkers for several decades, and they have been essential to the management of GH-treated patients and patients with acromegaly (17, 34). Improvements in assay sensitivity and specificity and standardisation over the subsequent years have been helpful, but markers more closely linked to efficacy and safety endpoints are still needed (35).

Paediatric indications

In paediatrics, there is currently an unmet need for better predictors of GH treatment efficacy in relation to linear growth response, metabolic benefit and safety. There is a need for biomarkers that reflect therapeutic response in specific tissues such as the growth plate and skeleton in a variety of disorders associated with short stature. (36).

Adult GH replacement

Serum IGF-I primarily reflects GH action in the liver (37), but its relationship to clinically meaningful efficacy endpoints such as measures of body composition is limited in individual patients (38). Other GH-responsive biomarkers can be measured, such as bone turnover markers, but the long-term value of their measurement in clinical practice is unknown. There is a major need for biomarkers that reflect the diverse effects of GH therapy on carbohydrate, protein and lipid metabolism as well as QoL in a dose-dependent manner.

Acromegaly

The ideal biochemical biomarker of efficacy should accurately reflect disease activity and be independent of treatment modality. As with adult GHD, there is a need for biomarkers that reflect improvement of metabolic status during therapy. There is also a need for a biomarker to predict optimal response to therapy, especially in circumstances when GH and IGF-I are discordant.

Potential candidates

A number of GH-responsive markers including matrix metalloproteinases 2 and 9, vascular endothelial growth factor, isoforms of apolipoprotein A-1 and haptoglobin and afamin have been identified (39, 40, 41). Their usefulness as biomarkers should be established in future studies. GH doping detection strategies have highlighted proteins such as procollagen Type III N-peptide and other bone markers in serum that may have utility in acromegaly management in the future (42, 43). A pharmacogenomic study has identified genetic biomarkers of responsiveness to GH treatment of children with GHD or Turner syndrome, which seems a promising future tool (44). In addition, circulating levels of a degradation fragment of type X collagen, which is a by-product of endochondral ossification, may provide a tool to monitor growth in paediatric patients (45).

Conclusion

Adult height remains the clinical endpoint of GH treatment in paediatric patients, and height velocity during the first and second year after treatment initiation is useful surrogate endpoints. In adult GHD patients, a reduction in truncal fat mass is typically the main clinical efficacy endpoint for regulatory purposes, but
improvement in QoL and physical fitness are also used in clinical practice. Lowering of elevated IGF-I levels in combination with symptom relief are efficacy endpoints used both for regulatory approval of novel drugs for acromegaly treatment and in clinical practice. Serum IGF-I is above all the most widely used biochemical biomarker during GH treatment as well as in acromegaly (Table 1); nonetheless, serum IGF-I correlates only weakly with clinical endpoints of efficacy.

There is an unmet need for novel biomarkers within the field of GH treatment and acromegaly. Systems medicine approaches using genomics, epigenomics, metabolomics and proteomics may facilitate selection of patients for therapy and improve prediction of clinical endpoints. Therefore, such approaches deserve further study, and the collection of suitable samples for biobanking should be considered in relevant clinical trials. The identification of novel biomarkers for action of GH requires access to samples from prospective controlled interventional trials. At present, numerous large-scale studies are being undertaken to examine the efficacy of LAGH preparations and new treatments for acromegaly, which provide the ideal opportunity to prospectively identify such novel markers.

Declaration of interest

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Disclaimer
The views expressed in this article are personal and not necessarily the views of the European Medicines Agency, the Committee for Medicinal Products for Human Use or the Medical Products Agency.

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