Editorial

Advances in Pediatric Growth Hormone Therapy: IGF-I-based Dosing

Various hormonal therapeutics, which emerged over the past two decades, revolutionized the course of pediatric endocrine disease. Recombinant human growth hormone (rhGH) application in management of pediatric disorders involving poor growth and abnormal body composition allowed remarkable outcomes in management of not only growth hormone deficiency (GHD) but also Turner syndrome, Prader-Willi syndrome, idiopathic short stature (ISS), small for gestational age (SGA), and chronic renal failure.

Once daily subcutaneous injection of GH is the recommended mode of GH therapy and is uniformly applied by pediatric endocrinologists. Dosing of GH however, is a more challenging issue, because of various factors, which involve both efficacy and safety. This is particularly true for the newer indications such as ISS. These patients have variable degrees of responses to GH therapy requiring not uncommonly higher doses of GH to promote optimal linear growth.

GH dosage strategies

GH dose has been traditionally selected based on body weight and monitored using linear growth velocity. Expanding of GH therapy for conditions with primary metabolic dysfunctions such as Prader-Willi syndrome or conditions with short stature and poor growth without any demonstrable hormone deficiencies such as Turner syndrome, ISS or SGA, has given rise to alternate parameters for assessing adequacy of the GH dose.

Evolution of insulin-like growth factor-I(IGF-I) as a parameter in GH dosing: the ISS model

ISS describes a diverse group of patients with short stature and poor growth without any demonstrable hormone deficiencies or systemic illnesses. Several studies confirm the overall efficacy of GH therapy in increasing adult height in these patients.

Rogol, *et al.*(1) demonstrated an increase of 1.2 height-SDS units in ISS children treated for 2-6 years with GH, comparable to an increase of 1.3 height-SDS units observed in GHD children. Hintz, *et al.* showed that children with ISS treated with GH for 2-10 years achieved a mean change in height of + 1.3 SDS, resulting in a significant increase in adult height above their predicted adult height, and above the adult height of untreated control ISS children(2). In the randomized, placebo-controlled trial by Leschek, *et al.* 4 years of GH treatment increased adult height in peripubertal children with ISS, with a mean height gain of a mere 0.5 SDS, (3.7 cm) over the placebo group, however this outcome might have been influenced by the dosing of GH, which was lower than the current standard recommendations and was dosed 3 times per week rather than daily(3). Finkelstein et al reported a better outcome(4), with an average adult height gain of 4-6 cm with long-term treatment in patients with ISS.

GH-naïve patients with ISS demonstrate variable IGF-I levels. The data from the National Cooperative Growth Study (NCGS)

examining prepubertal GH deficient and ISS patients, demonstrated an inverse correlation between pre-treatment IGF-I levels and the first-year change in height-SDS with a higher growth response predicted by a lower baseline serum IGF-I. However, among patients with the lowest IGF-I levels, only patients with GHD demonstrated an excellent response to GH therapy. GHD patients with the lowest IGF-I levels achieved a first-year height SDS increase of 1.5-2.0 SDS or greater. The mean values of first year change in height SDS for the GHD group were 0.77 SDS compared to 0.60 SDS for the ISS group. These patients, it should be noted were treated with standard weight-based doses of GH. It was suggested that the less favorable response in ISS patients might indicate partial GH insensitivity and that these patients require higher GH doses.

IGF-I-monitoring during GH therapy

The independent correlation between the gain in height SDS and on-treatment IGF-I levels reported recently indicates that growth response may be determined by the circulating IGF-I level, rather than GH dose *per se*.

Cohen, *et al*. studied the effect of GH dose and gender on growth in pre-pubertal GH-deficient children(5). Patients were randomized to low-, medium- and high-dose GH (25, 50 and 100 mcg/kg/day) for 2 years. Serum levels of IGF-I and Insulin-like growth factors and their binding protein-3 (IGFBP-3) were independently correlated with the change in height SDS: patients with higher IGF-I levels, regardless of their GH dose, had more rapid growth. Additionally, change in height SDS showed dependence on the GH dose, as did serum IGF-I and IGFBP-3 levels. Prepubertal gender differences in GH sensitivity were also found with males showing a linear growth response with increasing GH dose, whereas females had a plateau of both linear growth and IGF-I SDS at and above 50 mcg/ kg/day.

Mauras, *et al*.(6) randomized pubertal GH-deficient children to standardized dosing of 43 mcg/kg/day or 100 mcg/kg/day for 3 years. Serum IGF-I levels were measured at baseline and every 3 months. The high-dose group had significantly greater increases in growth and near-adult height as well as IGF-I levels compared with the standard dose group. Even though IGF-I levels were significantly higher in the high dose group, there was no statistical significance between the treatment groups regarding occurrence of adverse events and this study established the safety and efficacy of high-dose GH in pubertal children with GH deficiency.

In a study by van Teunenbroek, *et al*. the effects of variable GH dosing in pre-pubertal Turner syndrome patients were studied(7). The independent, positive correlation between height SDS and serum IGF-I levels was found. Patients with higher IGF-I levels, regardless of their GH dose, had more rapid growth.

Kamp et al studied GH dosing regimen in pre-pubertal children with ISS(8). The patients received three different GH doses: 17, 34 or 68 mcg/kg/day with washout periods between dose changes. The change in IGF-I SDS on the high dose regimen correlated with the change in height SDS, similarly to the result reported by Cohen(5) in GH-deficient children and in van Teunenbroek's study with Turner syndrome patients(7).

It has been suggested by Park and Cohen in a recent review(9) that individual sensitivity to GH treatment, as manifested by serum IGF-I levels achieved during therapy, plays a key role in growth response during treatment across different subpopulations of patients treated with GH. They proposed a

model for multiple-phase GH dosing in children, with treatment goals that include target IGF-I Z-scores and side effects monitoring. They proposed pursuing a target of IGF-I Z-scores of +2 to +3 SD for catch-up growth to maximize height and a target of –1 to +1 SDS for maintaining growth during childhood; and again a target of +1 to +3 IGF-I SDS in puberty to optimize final height; 0 to +1 SDS in transition period to maintain bone health and body composition. Park and Cohen clearly contradicted the previous one-size-fits-all approach by proposing this IGF-based dosing strategy, which should allow addressing the inter-individual variability in GH responsiveness. This model proposes to optimize both the safety and efficacy of GH therapy.

Several recent studies have demonstrated a dose-response effect of GH on growth factors levels in children with various conditions and have established the safety and efficacy of GH doses up to 100 mcg/kg/day. GH and IGF-I levels demonstrated significant independent effects on increase in height SDS in GH deficient pubertal children, which promoted higher GH dose to be used in puberty. IGF-I based GH dosing allowed continua-tion of GH therapy through adulthood by a transition from the higher growth-promoting dosing to maintenance dosing for normal body composition and metabolism. According to the model of Park and Cohen(9), titration of the GH dose during the rapid phase of growth to the range of +2 to +3 SDS should optimize linear growth velocity while during the maintenance dosing phase IGF-I levels can be kept at the middle of the normal range.

Safety implication of IGF-I monitoring during GH therapy:

IGF-I-monitored GH therapy allows avoidance of theoretical side effects such as metabolic or malignant diseases. Studies have shown that normalization of serum IGF-I levels with surgical or pharmacological therapy in acromegaly ceases progression of cardiomyopathy(10) and correlates with survival rate. Additionally, studies in GH-deficient adults showed that if supra-physiologic levels of IGF-I were avoided, a reduction in occurrence of edema and arthralgias was apparent.

One of the most important concerns in GH therapy is excess GH and IGF-I exposure and the possibility of an increased malignancy risk. It has been demonstrated that IGF-I has mitogenic properties and is a known inhibitor of apoptosis and certain adult cancers have been epidemiologically related to the pre-diagnostic IGF-I level(11,12). True causality between IGF-I levels and malignancy has not been established and a higher malignancy risk in the pediatric population treated with GH has not been reported. However, monitoring of IGF-I and IGFBP-3 levels during GH therapy is recommended(13).

Thus, a modern approach to GH dosing should utilize an algorithm that integrates GH dosing strategies based on, diagnosis, weight, IGF-I level, and growth velocity. The approach proposed by Park and Cohen is outlined as follows:

(1) Administer GH initially by the standard weight-based, diagnosis appropriate, approved dose.
(2) Adjust the GH dose based on IGF-I level, aiming for specific growth-phase-specific targets, which will compensate for variability in GH absorption, distribution, metabolism, excretion and most importantly, the variability in GH sensitivity,
(3) Monitor growth velocity and apply growth velocity-based dose adjustment

to optimize final height.

Summary

IGF-I monitored GH therapy is an important emerging tool to insure safety and efficacy of GH. It also identifies patients who have GH insensitivity and may benefit from other therapies. IGF -I monitoring and growth velocity response should be synergistically utilized in GH therapy to maximize the risk-benefit ratio and cost-effectiveness.

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