IGF-I therapy in growth disorders

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Abstract

Patients with GH insensitivity, typically resulting from mutations affecting the GH receptor (GHR), GHR signaling cascade, or the *IGF-I* gene, are, generally, unresponsive to GH therapy. Beginning in the 1990s, clinical trials of IGF-I administration in such patients demonstrated both short- and long-term efficacy, although not to the degree observed with GH treatment of naïve GH-deficient patients. Adverse effects, including hypoglycemia, lymphoid overgrowth, benign intracranial pressure, and coarsening of facial features, have been observed, but, in general, have proven to be transient. As interest in the potential efficacy of IGF-I treatment for children currently labeled as idiopathic short stature increases, it will be important to have controlled clinical trials of GH, versus IGF-I versus combination, GH + IGF-I.

European Journal of Endocrinology 157 S57–S60

Since initial observations of patients with growth hormone insensitivity (GHI) in the 1960s, it has been evident that GH therapy will not be clinically effective in all patients with low serum insulin-like growth factor-I (IGF-I) concentrations (1, 2). As our understanding of the GH–IGF axis expanded, it became reasonable to classify children with growth failure and inappropriately low serum IGF-I levels as IGF deficient (IGFD), and, additionally, divide such cases into secondary and primary forms, as has been the custom with other endocrine disorders such as hypothyroidism, hypocortisolism, and hypogonadism (3). Thus, patients with low serum IGF-I associated with low GH concentrations are considered to have secondary IGFD, reflecting a defect in pituitary production of GH (on either a hypothalamic or pituitary basis), while children with short stature and low serum IGF-I, despite normal or increased GH levels, are classified as primary IGFD.

The molecular basis of primary IGFD has broadened significantly since the first reports of GHI by Laron and colleagues (1, 3). Over 250 cases of defects involving the GH receptor gene (*GHR*) have been reported to date. These include more than 60 different mutations of *GHR*, affecting the ability of the receptor to bind GH, dimerize, anchor in the cell membrane, migrate to the cell

membrane, or initiate post-receptor signaling. Six cases of homozygous mutations of the signal transducer and activator of transcription (*STAT*)-5*b* gene have also been described (4). From an auxological perspective, these cases appear indistinguishable from patients with GHR defects, supporting the critical role of *STAT5b* in linking the GHR with IGF-I production. Three patients have been described with mutations or deletions of *IGF-I*, including two cases of bioinactive IGF-I, where missense mutations have resulted in IGF-I molecules with decreased affinity for the IGF-I receptor (5, 6). Finally, several cases have been reported of mutations of the gene for the acid labile subunit (*ALS*), which encodes a protein which forms part of the ternary complex that transports IGF-I in serum (7,8). These cases, while having markedly low serum IGF-I concentrations, appear to have only modest growth failure, presumably reflecting relatively normal free IGF-I in serum or IGF-I delivery to target tissues.

While secondary IGFD is, typically, highly responsive to GH therapy (with the rare exception of patients developing anti-GH antibodies), patients with severe primary IGFD, reflecting serious defects in IGF-I production, generally show no or marginal responses to GH, even at pharmacological doses. As would be expected, individuals with molecular defects of the *GHR*, *STAT5b*, or *IGF-I* genes generally already have elevated GH production and are unlikely to respond to treatment with additional GH. Such patients are destined for adult heights ranging from –5 to –11 standard deviations below the mean, unless alternative therapeutic approaches are developed.

This paper was presented at the Ipsen symposium, 'The evolving biology of growth and metabolism', Lisbon, Portugal, March 16–18, 2007. Ipsen has supported the publication of these proceedings.

IGF-I therapy

In the 1990s, four clinical trials of IGF-I therapy, primarily in patients with confirmed or suspected GHR defects, were conducted: 1) Israel, where the original Laron dwarf patients were identified (9); 2) Ecuador, where the largest cohort of GHI patients was identified (10); 3) Europe (11); and 4) North America (12). All of these studies were largely uncontrolled, the major exception being a placebo-controlled, blinded trial in Ecuador (10). Despite some variation in patient inclusion criteria, as well as minor protocol and IGF-I dosage differences among the studies, the findings were highly consistent: first-year growth rates increased from a pre-treatment mean of 3–5 cm/year to 8–9 cm/year in year 1, with progressive attenuation in subsequent years. Relatively long-term results are available from two studies, Europe, and North America, and, again, show considerable consistency (11–13). In the European study, IGF-I was given at dosages ranging from 40 to 120 µg/kg twice a day (11). In the larger North American study, most subjects received 120 µg/kg twice a day after the first year of therapy, when the IGF-I dosage ranged from 40 to 120 µg/kg (12,13). A modest, but significant dose dependency was observed during that first year of therapy. These findings differ somewhat from an earlier report from Ecuador, which showed no difference in 1- and 2-year growth responses to 80 vs 120 µg/kg twice a day (9). Since the Ecuador study was confined to patients homozygous for a severe mutation of *GHR*, characterized by markedly reduced serum concentrations of not only IGF-I but also IGF-binding protein-3 (IGFBP-3) and ALS, it is not entirely clear whether the lack of differential response to IGF-I dosage reflects limitations induced by the low serum levels of IGFBPs.

The North American study has proven to have the greatest body of long-term data, although results largely corroborate smaller studies from Ecuador, Europe, and Israel (Table 1) (9–13). Seventy-six children with primary IGFD, principally patients with GHR defects, were treated with IGF-I for up to 12 years in a largely

open-label study design. Height velocity increased from pre-treatment mean of 2.8 cm/year to an average of 8.0 cm in year 1. In patients receiving IGF-I doses of at least 100 µg/kg twice a day the mean year 1 growth rate was 8.7 cm. Subsequent years showed the anticipated progressive deceleration, although mean growth rates remained significantly above baseline.

Despite these excellent results, all studies to date have shown that growth rates achieved with IGF-I treatment, although significantly greater than pre-treatment values, fail to match the growth rates achieved with GH therapy of naïve GH-deficient (GHD) patients. Whether expressed as mean height velocity, δ height velocity over baseline, or δ height SDS, IGF-I Rx fails to parallel results with GH therapy of GHD (9). A variety of explanations have been proposed: 1) failure to identify optimal IGF-I dosage; 2) failure of IGF-I treatment (unlike GH treatment of GHD) to normalize the typically low serum concentrations of IGFBP-3 and ALS, resulting in rapid clearance of administered IGF-I; 3) failure of injected IGF-I to fully reach the epiphyseal growth plate, compounded by the potential ability of GH to stimulate local production of IGF-I in epiphyseal chondrocytes; and 4) possible IGF-independent actions of GH on skeletal growth. Although it may be premature to judge, preliminary (and uncontrolled) results with administration of complexes of IGF-I:IGFBP-3 show extension of the half-life of serum IGF-I, but fail to display any improvement in growth rates over that observed with IGF-I alone (14, 15). These observations would seem to imply that the failure of IGF-I to fully duplicate GH's effect on skeletal growth reflects IGF-independent effects of GH and/or the ability of GH to induce local production of IGFs at the epiphyses.

Adverse effects of IGF-I

Patients whose underlying condition is one of GH resistance, especially if it is complete and at the level of the GHR, having lost the counter-regulatory effects of GH, are susceptible to hypoglycemia (2). A number of studies have indicated that as many as 50% of such patients, especially the younger ones, have histories of spontaneous hypoglycemia (2). In this context, it has become difficult to assess the incidence of IGF-I-induced hypoglycemia, although it is certain that the latter has been observed, including seizures. It has been reported that the administration of IGF-I with meals largely eliminates the occurrence of hypoglycemia (J Guevara-Aguirre, personal communication), although it is still recommended that this risk be discussed fully with parents (especially of young children) and that they be instructed in its prevention and management.

Most of the other adverse effects appear to be related to hyperstimulation of lymphoid tissue growth: tonsillar growth, snoring, sleep apnea, recurrent ear infections, thymic hypertrophy, and splenic enlargement (the latter

Table 1 Long-term results of insulin-like growth factor-I (IGF-I) treatment.

Years on IGF-I	Ranke <i>et al.</i>		Chernausek <i>et al.</i>	
	<i>n</i>	cm/year	<i>n</i>	cm/year
1	15	8.8	59	8.0
2	13	7.0	54	5.9
3	12	6.8	48	5.5
4	15	5.0	39	4.8
5	13	5.2	21	4.9
6	6	6.3	20	5.0
7			16	4.7
8			14	4.6

Ranke *et al* (11); Chernausek *et al* (13).

two being, typically, asymptomatic) (10–13). Injection site hypertrophy has been observed, but is generally amenable to proper rotation of injection sites. Arthralgias and myalgias have been reported in as many as 20% of recipients in uncontrolled studies, but are usually transient. Benign intracranial hypertension has been reported in ~4% of recipients. Although this number appears somewhat larger than that observed with GH treatment, it is usually transient, disappearing following temporary cessation of treatment.

Craniofacial growth, sometimes with coarsening of features, has been described in a number of patients (10–13). While sometimes seemingly dramatic, the absence of long-term controlled studies makes these observations difficult to quantify and assess. Many of these patients have baseline craniofacial disproportion, with undersized faces; in such patients, some 'over-development' of the maxilla, mandible, and midface may be welcome. It must be recognized, also, that coarsening of facial features is part of normal pubertal maturation and, probably represents a normal, physiological, IGF-I-mediated event of adolescence. In any case, in most situations where IGF-I therapy has been associated with such coarsening, the results appear to 'soften' with time and do not appear to lead to any permanent disfigurement.

Future directions in therapy

IGF-I has now been approved by the Food and Drug Administration for treatment of severe primary IGF-I deficiency, which has been arbitrarily defined as a height < -3 S.D., accompanied by a serum IGF-I < -3 S.D., despite normal GH concentrations. It should be recognized that this decision was not based upon studies specifically directed at this population, but, rather, reflects a reasonable compromise between the desire to offer treatment to children with unequivocal GH insensitivity, while not, as yet, opening the entire ISS population to the possibility of IGF therapy.

It is clear, nevertheless, that the ISS population represents a heterogeneous group, many of whom are likely to have some degree of GH resistance (16). As many as 25% of children labeled as ISS have low serum IGF-I concentrations, despite normal GH levels. It is likely that as our understanding of the molecular basis of IGFD expands, genetic defects will be identified in many such patients. While studies have indicated that such patients may respond to increasing dosages of GH, the long-term costs and risks of such approaches have not been adequately evaluated to date. Accordingly, many of these patients may prove to be appropriate candidates for IGF-I treatment. It is certain that this is an area that cries out for carefully controlled prospective trials of GH versus IGF-I and, possibly, combination GH + IGF-I. Whether therapy is to be with IGF-I or with increasing dosages of GH, consideration must be given

to wards determining what maximal serum concentrations of IGF-I that are acceptable, as well as to long-term risks.

It is also of note that low serum concentrations of IGF-I in the face of normal or elevated GH levels may be observed in children with nutritional deficiencies, chronic inflammatory processes, and some chronic diseases. The possibility of such underlying conditions needs to be assessed in all children presenting with growth failure. Future clinical studies of the potential efficacy of IGF-I therapy in some such conditions should be considered.

It has been said that, 'if all you have is a hammer, everything looks like a nail'. For decades, GH has been the pediatric endocrinologist's 'hammer'. It now appears that we have a few more tools in the endocrine toolchest. Now, we simply must learn to use them properly.

Disclosure

This paper forms part of a *European Journal of Endocrinology* supplement, supported by Ipsen. The author discloses: Ron G Rosenfeld: only relationship with Ipsen was to receive an honorarium for talks given at a symposium. No equity position. This article was subject to rigorous peer review before acceptance and publication.

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Received 22 March 2007

Accepted 18 June 2007