The Role of Recombinant Human Insulin-Like Growth Factor-I in Treating Children with Short Stature

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Context: Recombinant human (rh) IGF-I is now available to treat children with short stature resulting from severe primary IGF-I deficiency. This review from the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society discusses different aspects of rhIGF-I therapy, particularly with regard to potential advantages and disadvantages in comparison with the traditional use of rhGH for treatment of short stature.

Evidence Acquisition: We used the Entrez-PubMed search engine to conduct a review of publications addressing IGF-I deficiency, the use of rhIGF-I, and treatment for short stature.

Evidence Synthesis: rhIGF-I, as a twice-daily sc injection, is now approved for treatment of short stature in children with severe primary IGF-I deficiency, which may occur as a consequence of mutations in the GH receptor, defects in the post-GH receptor signaling pathway, and IGF-I gene defects. It is also approved for children with GH deficiency who develop neutralizing antibodies to GH. rhIGF-I significantly improves growth in these conditions. However, adult height may still be suboptimal, possibly due to lack of direct GH effects. Dosing regimens for rhIGF-I administration are under investigation, as are other indications for use of rhIGF-I.

Conclusion: The use of rhIGF-I is justified in conditions approved by the Food and Drug Administration. Until more substantial data become available, the use of rhIGF-I outside Food and Drug Administration recommendations should only be investigational. **(*J Clin Endocrinol Metab* 93: 10–18, 2008)**

Commercial availability of recombinant human (rh) IGF-I has added to the choice of agents that can be used to treat children with short stature. Over the years, approved indications to treat short children with rhGH have increased. In addition to GH deficiency (GHD), rhGH is now used to treat children with Turner syndrome, SHOX haploinsufficiency, Prader-Willi syndrome, chronic renal failure, idiopathic short stature (ISS), and those who were small for gestational age with persistent growth failure. rhIGF-I was approved by the Food and Drug Administration (FDA) in 2005 and the European Agency for the Evaluation of Medical Products (EMEA) in 2007 for use in conditions of severe primary IGF-I deficiency (see definition below) due to genetic GH resistance or insensitivity (GHI), and GH gene deletions with development of neutralizing antibodies to GH. Studies are currently ongoing to investigate possible benefits from rhIGF-I therapy in less severe IGF-I deficiency (http://www.tercica.com/medical/condition/what.html) and X-linked severe combined immunodeficiency, and with rhIGF binding protein (IGFBP)-3 in severe forms of insulin resistance such as leprechaunism and type A insulin resistance syndrome (1). Previously published studies demonstrate beneficial effects of rhIGF-I treatment alone in conditions of leprechaunism (2) and rhIGF-I with or without IGFBP-3 in increasing insulin sensitivity in diabetes mellitus (3, 4), although concerns of potentially worsening retinopathy have led to a discontinuation of these trials. Animal and small pilot studies demonstrated beneficial effects of rhIGF-I given alone or with rhIGFBP-3 in liver disease, neurological disorders or injury, and critical illnesses (5–8). The com-

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Abbreviations: ALS, Acid labile subunit; CDGD, constitutional delay of growth and development; GHBP, GH binding protein; GHD, GH deficiency; GHI, GH insensitivity; GHR, GH receptor; IGFBP, IGF binding protein; ISS, idiopathic short stature; rh, recombinant human; SDS, SD score.

bination of rhIGF-I+rhIGFBP-3 was commercially available for a short period of time but is no longer available for the treatment of short stature as part of a legal agreement (further discussion to follow). There is a growing concern among pediatric endocrinologists about indiscriminate use of rhGH and rhIGF-I for less severe short stature without adequate consideration of economic, social, or psychological costs attendant on medicalizing normal variation. These considerations are in addition to the traditional therapeutic concerns of safety and efficacy and the risk to benefit ratio. The goal of this review was to briefly summarize the physiology of the GH-IGF axis and describe available data and unanswered questions regarding the use of IGF-I for growth promotion in pediatric patients.

The GH-IGF System

GH has important metabolic functions and overall creates conditions for anabolism. In the context of statural growth, it exerts direct effects at the growth plate and indirect effects through the production of IGF-I.

GH

GH is a single chain polypeptide produced by the somatotroph cells of the pituitary gland (9, 10). In the circulation, GH binds to GH binding protein, which is the extracellular component of the GH receptor (GHR). Low serum levels of GH binding protein may represent deficiency of the GHR, a known cause of GH insensitivity (Laron syndrome).

GH binds to its receptor and stimulates growth by acting at two main sites: the liver and growth plate. In the liver GH stimulates production of IGF-I, IGFBP-3, and acid labile subunit (ALS). At the growth plate, GH stimulates proliferation of prechondrocytes and production of IGF-I (11). Direct effects of GH at the growth plate and effects of both systemically and locally produced IGF-I are thought to be necessary for optimal linear growth (12).

IGF-I

IGF-I, previously known as sulfation factor or somatomedin-C, is a mediator of GH action and a stimulator of somatic growth. The structure of IGF-I is 70% homologous to that of IGF-II and 50% homologous to proinsulin (13). IGFs are potent mitogenic agents and their actions are determined by the availability of free IGFs to interact with IGF receptors. The rate of IGF production, clearance, and degree of binding to the IGFBPs modulate levels of free IGFs in a system (14, 15).

Although the liver is the main source of circulating IGFs, physiologically important production of IGF-I occurs in other tissues, including the growth plate and bone, with various autocrine and paracrine functions (14, 15). In serum, most of the IGF-I is found in the ternary complex, formed by IGF-I, IGFBP-3, and the glycoprotein known as ALS (16, 17). Only a small amount of IGF-I is carried by IGFBPs as a binary complex, and less than 1% circulates in the free form. The ternary complex, with a molecular mass of 150 kDa, does not cross the capillary barrier, and ALS is found only in the intravascular space (18). The formation of the ternary complex protects and consequently prolongs the half-life of both IGFBP-3 and IGF-I. The circulating half-lives of unbound IGFBP-3 and IGF-I are very short, between 30 and 90 min for IGFBP-3 and less then 10 min for IGF-I. Conversely, the half-life of the ternary complex is much longer at approximately 12 h (19). The binding of IGF-I to IGFBP-3 and ALS maintains IGF-I in the intravascular space for steady delivery to target tissues, in contrast to the pulsatile levels of GH. IGFBP-3 not only extends the serum half-life of IGF-I but also has a role in its distribution. At the tissue level, due to the absence of ALS, most of the IGFs are bound to the IGFBPs as a heterodimer, with only a small amount found in the free form.

The liver is the main source of circulating IGFBP-3 and ALS. IGFBP-3 is produced by the hepatic endothelial and Kupffer cells, whereas ALS and IGF-I are produced by hepatocytes (20–22). The hepatic production of the ternary complex is regulated by GH (23), with reduced serum levels of all three components in GHD or GHI and elevated levels in conditions of GH excess such as gigantism and acromegaly (24–28). Serum levels of IGF-I are age dependent with low levels at birth, peak levels during puberty, and a steady lowering of levels with increasing age (29). Serum levels of IGF-I are low in not only GHD and GHI but also malnutrition, catabolic states, and some chronic diseases (30).

Prenatal growth is independent of GH but is highly dependent on IGF-I and IGF-II. Postnatal growth depends on the production of GH and IGF-I (31, 32). Knockout animal models demonstrate that the association of GHD with IGF-I deficiency affects growth more than IGF-I deficiency alone, indicating that GH has growth-promoting activities independent of IGF-I (33). Supporting this concept, studies with hypophysectomized rats have also shown that the growth response to GH therapy is greater than the response to therapy with IGF-I (34).

IGFBPs

There are six IGFBPs that bind to IGFs with high affinity and specificity. IGFBPs are produced by a variety of tissues, with each tissue having specific levels of several IGFBPs. The IGFBPs have several functions: 1) prolongation of the half-life of IGF-I in the circulation, 2) prevention of IGF induced hypoglycemia, 3) regulation of the passage of IGFs from the intravascular to the extravascular space, 4) limitation of the bioavailability of free IGFs to interact with IGF receptors, 5) enhancement of IGFs actions by the formation of a pool of slow release IGFs, and 6) direct cellular actions mediated through their own receptors, acting independently of IGFs (15).

As with IGFs, serum levels of IGFBP-3 are age dependent, being low at birth and increasing during childhood to reach peak levels during puberty, after which they begin to decrease.

Children with Low Serum Levels of IGF-I

Low serum levels of IGF-I can be associated with low, normal, or elevated GH levels. Patients with short stature, low growth velocity, delayed bone age, low serum levels of IGF-I and IGFBP-3, and low serum levels of GH after two different stimulation tests are considered GH deficient. These children need to have addi-

tional evaluation of pituitary anatomy and function and typically respond well to rhGH therapy with acceleration of linear growth and attainment of normal adult height, particularly when stimulated GH levels are very low. Of note, when stimulated GH levels of less than 10 ng/ml are used to define GHD, more than 30% of children have a growth increment of less than 0.5 SD score (SDS) in the first year of therapy (35). It is important to differentiate GHD from constitutional delay of growth and development (CDGD), although this distinction may sometimes be difficult. Children with CDGD may have short stature, low growth velocity, delayed bone age, low response to GH stimulation tests, and low IGF-I and IGFBP-3 in the pre- and early pubertal period, compared with normal values for age (36, 37). Typically the values are normal when corrected for bone age. Children with CDGD are considered for treatment when pubertal delay is severe, with psychosocial implications. The use of low-dose sex steroids for a short period of time has been demonstrated to accelerate the pubertal process without affecting adult height (36–39).

Patients with short stature, delayed bone age, low serum levels of IGF-I, and normal or elevated serum levels of GH are not considered GH deficient. They may have malnutrition, which need not be obvious, certain chronic diseases, or GHI. Consequently, in the evaluation of children with short stature and low serum levels of IGF-I, it is important to look for evidence of chronic disease and inadequate nutrition. It is also important to consider use of medications for treatment of attention deficit disorders.

In patients with a normal GH response to provocative testing, the IGF-I or IGFBP-3 generation test could be helpful in differentiating between low serum levels of IGF-I that are responsive, or partially responsive to rhGH, from low serum levels of IGF-I that do not respond to rhGH administration with an increase in IGF-I levels and would not be expected to respond to rhGH treatment with an improvement in linear growth and adult height (40–43). The IGF-I generation test assesses IGF-I levels after administration of rhGH. As an example, one of the published protocols describes the use of a dose of 0.033 mg/kg·d of rhGH for 4 d and diagnoses GHI when there is an inadequate increment in IGF-I or IGFBP-3 levels. However, the necessary increment in IGF-I or IGFBP-3 levels for a positive test is still a matter of debate, with different authors suggesting different values and also different methods to determine an adequate response (41, 44, 45) and quite often using different IGF-I assays. In addition, there is controversy regarding the appropriate dose of rhGH to use for this test. For instance, Cotterill *et al.* (46) reported that 0.033 mg/kg·d of rhGH in the IGF-I generation test does not identify mild GHI in children with ISS, raising concerns that the standard test may deliver a supraphysiological dose of GH. Blair *et al.* (47) suggested that a low dose IGF-I generation test may be more useful than the standard dose test in diagnosing mild cases of GHI. The low-dose test measures IGF-I and IGFBP-3 levels after 4 d of rhGH administered at a dose of 0.011 mg/kg·d. These authors also suggested that IGF-I levels be measured after 36 h (rather than 96 h) of initiating rhGH at the standard dose (0.033 mg/kg·d). In both tests, a positive response to GH is defined as a change in IGF-I or IGFBP-3 levels that is more than twice the coefficient of variation of the assay used. This test was validated to identify severe forms of GH insensitivity.

Because of controversies regarding the optimal protocol, diagnostic interpretation, lack of assay standardization, and nearly no correlation of test results with the clinical response to rhGH, there is a need for more studies in this area. Even though IGF-I generation tests could potentially determine which patients should receive GH alone, IGF-I alone, or a combination of GH and IGF-I (discussed subsequently), at the current time, it is impossible to recommend a particular protocol for the routine clinical conduct of IGF generation tests.

Treatment of Short Stature and Low Serum Levels of IGF-I

Table 1 classifies the possible etiologies for low serum levels of IGF-I based on the observed or expected response to therapy with rhGH and/or rhIGF-I. Clinical features and anthropometrical and laboratory data should differentiate whether these children need any form of therapy at all and which is the optimal therapy to use.

There are several options for the treatment of these children, depending on diagnosis, severity, and age, including improving nutrition or care of chronic illnesses, use of androgens, aromatase inhibitors (not FDA approved), rhGH, or rhIGF-I. An in-depth discussion regarding the use of androgens, aromatase inhibitors, and human GH is beyond the objectives of this review, but it is important to point out that therapy of GH-deficient children with rhGH successfully improves growth and normalizes adult height (35, 48, 49).

Until March 2007, there were two formulations of rhIGF-I in the United States: isolated rhIGF-I (Increlex, mecasermin; Tercica Inc., Brisbane, CA) and the binary protein complex of rhIGF-I and IGF-I binding protein-3 (iPlex, mecasermin rinfabate; Insmed Inc., Glen Allen VA). In March 2007, Tercica and Insmed entered an agreement that resolved that Insmed would no longer provide rhIGF-I+rhIGFBP-3 to patients with severe primary IGF-I deficiency and other short stature indications. Insmed would, however, have freedom to manufacture, develop, and commercialize rhIGF-I+rhIGFBP-3 for certain non-short stature indications including severe insulin resistance, myotonic muscular dystrophy, and HIV-associated adipose redistribution syndrome (www.go-iplex.com.). Although the combination of IGF-I with IGFBP-3 is theoretically a better method of delivering rhIGF-I in that it would stabilize IGF-I, allow higher doses with less hypoglycemia and prevent rapid clearance, allowing greater delivery of rhIGF-I to target tissues, it is unclear whether clinically these purported advantages would result in greater effectiveness than rhIGF-I alone, and there are no back-to-back comparisons of rhIGF-I *vs.* combination therapy. A definite advantage of the combination of rhIGF-I with rhIGFBP-3 is that it is administered once daily, unlike rhIGF-I, which needs to be administered twice a day. There are, however, ongoing studies examining the efficacy of rhIGF-I administered once daily, although growth response in Israeli patients with GHI treated with

TABLE 1. Conditions associated with low serum levels of IGF-I classified based on proven or expected response to available treatment options

GH responsive	Genetic isolated GH deficiency	GHRH deficiency, GHRH receptor defects, GH1 gene defect
	Genetic multiple pituitary hormone deficiencies including GH deficiency	HESX1, LHX3, LHX4, SOX3, GLI2, PITX2, PROP1, PIT1 (POU1F1) gene defects
	Other causes of IGHD or MPHD	Congenital or acquired
	Bioinactive GH	
GH unresponsive-IGF-I responsive	Acquired GH-inhibiting antibodies (in patients with complete GH1 gene deletions receiving rhGH therapy)	
	Mutations in the GH receptor	Extracellular domain
		Transmembrane domain
		Intracellular domain
	Post GHR-receptor defects	JAK2
		STAT5b
		Other STATs
	IGF-I gene mutations	IGF-I deficiency
		Bioinactive IGF-I
GH unresponsive-IGF-I unresponsive[a]	IGF-I receptor mutations	
	Post-IGF-I receptor defects	
Response pattern unclear[a]	IGFBP-3 mutations	
	ALS mutations	
	Catabolic states	Trauma
		Postoperative states
		Malnutrition
	Chronic illnesses	Liver disease, chronic renal failure
		Inflammatory bowel disease, severe failure to thrive

ISS was not included in this table. JAK, Janus kinase; STAT, signal transducer and activator of transcription; IGHD, isolated GHD; MPHD, multiple pituitary hormone deficiency.

[a] Responsiveness should be investigated in controlled clinical trials.

single daily injections of rhIGF-I was substantially less than in European, U.S., and Ecuadorian studies using twice-daily injection (50). Evidence of lymphoid hyperplasia and GH suppression in patients with GHI treated with rhIGF-I alone suggests adequate (even excessive) IGF-I delivery to at least some target tissues, even when it is not coupled with IGFBP-3 (51, 52). In the physiological state, IGF-I binds not only IGFBP-3 but also ALS, yet ALS deficiency, based on two reported patients, does not seem to affect adult height despite being associated with very low IGF-I and IGFBP-3 serum levels (53, 54).

Approximately 150 children have been treated with rhIGF-I worldwide, most of whom had GHI and fewer than 10% had GH inactivating antibodies (55–57). Backeljauw and Underwood (51) published their experience with the long-term use of isolated rhIGF-I in eight patients with GHI syndrome. The mean height velocity increased from 4.0 cm/yr before therapy to 9.3 cm/yr in the first year, 6.2 cm/yr in the second year, and slowly decreased to 4.8 cm/yr after 3–6 yr of therapy with rhIGF-I. The mean height was −5.6 SDS before rhIGF-I treatment and improved to −4.2 SDS after 6 yr of therapy. Data from other studies regarding growth velocity after initiation of rhIGF-I therapy are similar. In studies using comparable dosages of rhIGF-I, growth velocity increment in the first year averaged 5.2–5.8 cm/yr (57, 58) and waned rapidly after the first year. Considering that adult height for untreated patients with GHI ranges between −4 and −10 SDS, therapy with rhIGF-I does improve growth, although it does not compensate completely for lack of GH action, similar to effects observed in animal models (34). Although much less information on adult height is available in rhIGF-I-treated patients than rhGH-treated patients, the response of children with GH resistance to rhIGF-I therapy is of lesser magnitude than is the response of GH-deficient children to rhGH therapy (51, 57–59), with respect to growth velocity and adult height.

For the group receiving rhIGF-I+rhIGFBP-3 at the rhIGF-I equivalent dose of 200 μg/kg·d, comparable with that of rhIGF-I-treated groups, the increment in growth velocity was only 3 cm/yr (from 3.4 to 6.4 cm/yr). When a higher dose was used (400 μg/kg·d), the growth velocity increased by 6.3 cm/yr (from 2.0 to 8.3 cm/yr) (60). It would appear that substantially larger amounts of IGF-I are required when administered in combination with rhIGFBP-3 to obtain a growth response comparable with that with rhIGF-I alone.

The suboptimal growth response with rhIGF-I, compared with rhGH, has been attributed to the following: 1) inability of rhIGF-I to increase IGFBP-3 and ALS levels causing decreased delivery of IGF-I to target tissues and rapid clearance from the circulation (although to prove this point, we would need data on treatment with the combination of rhIGF-I, rhIGFBP-3, and rhALS, compared with treatment with rhGH alone); 2) lack of GH-induced proliferation of prechondrocytes in the growth plate; 3) absence of GH-induced local IGF-I production at the growth plate; and 4) difficulty in using higher doses of rhIGF-I because of the risk of hypoglycemia. However, as noted above, lymphoid hyperplasia with rhIGF-I therapy indicates adequate drug delivery to at least some target tissues (51, 57).

Many studies have now demonstrated the efficacy of rhIGF-I

in increasing stature in conditions of low serum IGF-I in which rhGH administration is not effective, including GHR mutations, postreceptor signal transduction defects, GH gene deletions with inhibitory GH antibodies after GH treatment (55–59), and in a case report of IGF-I gene deletion (61), in which growth velocity increased over 1 yr of rhIGF-I therapy. These conditions are approved indications for rhIGF-I treatment.

Use of rhIGF-I in ISS

Even though rhIGF-I therapy is currently approved only for patients with severe IGF-I deficiency, data from the Increlex Growth Forum Database Registry, presented as a poster at the 2007 meeting of The Endocrine Society showed that as of December 31, 2006, 17% of enrolled patients were diagnosed as having ISS (62). This use of rhIGF-I is based on the supposition that subtle alterations in the signaling pathways of GH-GHR may account for ISS in children who have low IGF-I but normal GH levels. Criticism of this premise comes from the knowledge that even mild inability to produce the target hormone (in this case, IGF-I) should be associated with some elevation in the stimulatory hormone (GH), and the absence of significant GH elevations in these cases makes the possibility of GH insensitivity suspect. Attie *et al.* (63) found slight, but clinically insignificant, elevations in mean overnight GH concentrations (2.8 ± 1.1 *vs.* 2.3 ± 1.1 μg/liter) as measured by 12 h of frequent sampling in patients with ISS who had low IGF-I and GH binding protein (GHBP) concentrations, with serum levels of GHBP being a surrogate for the expression of the GHR. In this same population, Goddard *et al.* (64) found a few heterozygous polymorphisms in the GHR in 14 children with ISS and very low GHBP levels. These polymorphisms were not associated with short stature in other family members and were shown to have no functional significance using transfection studies. Of importance, whereas baseline IGF-I is a strong predictor of response to rhGH in patients with GHD (65), the response of ISS patients to rhGH varies. A recent report indicates that the most important factors in determining response to rhGH therapy in children with low IGF-I are the rise in IGF-I levels during therapy, the rhGH dose, and the degree of GH deficiency (66). Similar findings have been reported by other investigators (67, 68). The role for rhIGF-I administration in ISS patients is currently unclear. Studies need to demonstrate that in comparison with rhGH treatment, treatment with rhIGF-I: 1) is associated with greater increases in growth velocity and predicted adult height SDS and/or 2) is more cost effective and/or 3) is associated with fewer side effects.

At the present time, published data demonstrate that in animal models, treatment with IGF-I without GH does not stimulate growth to the same magnitude as when IGF-I is administered with GH, and in humans with GHI (GHR mutations, signaling pathway defects), the growth response to rhIGF-I is not of the same magnitude as the response of children with GHD to rhGH (51, 57–59). Consequently, in ISS, a significant increase in growth velocity and adult height in response to rhIGF-I therapy, compared with the response to rhGH, appears unlikely. It remains to be determined whether results of ongoing studies will demonstrate appropriate efficacy and safety of rhIGF-I use in ISS children who have low serum levels of IGF-I and whether the response will be equivalent, superior, or inferior to GH therapy of this condition. In these children, the combination of rhGH and rhIGF-I may theoretically increase the growth response when compared with either hormone used alone. Studies testing this hypothesis have not yet been undertaken. One last concern regarding the use of rhIGF-I in children with ISS not truly GH insensitive pertains to the suppression of GH secretion from increasing IGF-I concentrations as a consequence of increased negative feedback. Although not GH insensitive, these children could potentially demonstrate suboptimal growth responses akin to children with true GH insensitivity from an IGF-I-induced decrease in GH concentrations, leading to a lack of proliferation of prechondrocytes, and a lack of local release of IGF-I at the growth plate.

Safety Concerns

Infants and children with GHI have episodes of hypoglycemia that may be severe, similar to hypoglycemia seen with severe GHD. Unlike GH replacement therapy, which corrects the hypoglycemia of GHD, IGF-I injection may enhance the risk. IGF-I increases muscle glucose uptake and decreases hepatic glucose output (69–71), whereas GH has the opposite effects. Hypoglycemia has been the most common early adverse event, noted in 49% of subjects in the largest treatment study (57). A somewhat lower frequency of 31% was reported with use of rhIGF-I/rhIGFBP-3, although in a smaller and slightly older population observed over a shorter period of time (60). In a 6-month long placebo-controlled study, Guevara-Aguirre *et al.* (72) reported hypoglycemia in 67% of children receiving placebo and 86% of those treated with rhIGF-I, an insignificant difference. Monitoring of fingerstick blood glucose concentrations in 23 subjects residing on a research unit documented frequent hypoglycemia before breakfast and lunch even before IGF-I treatment was begun. With rhIGF-I treatment there was no increase in the frequency of blood glucose measurements less than 50 mg/dl in these patients. Five of the subjects participated in a crossover, placebo-controlled study for 6 months with a 3-month washout period, and fasting glucose measurements were performed three times a day for the entire 15-month study period. The percentage of glucose values less than 50 mg/dl was 2.6% in the placebo group and 5.5% in patients receiving rhIGF-I, not a significant difference, and values greater than 140 mg/dl were observed in 1.4% of patients in the placebo group and 3.9% of those receiving IGF-I, also not significant (57). In practice, hypoglycemia can usually be controlled with adequate food intake. Adolescents with low IGF-I and IGFBP-3 levels who were monitored for 24 h at the end of 2 wk of rhIGF-I administration had no symptoms of hypoglycemia throughout the study and no glucose measurement less than 60 mg/dl during the 24 h monitoring (73). Published data therefore do not support the idea that therapy with rhIGF-I increases the risk of hypoglycemia.

Lipohypertrophy at the injection site, which can reduce growth response, affects at least one third of patients and is

related to failure to rotate injections (57). Hair growth at the injection site has been described only with the rhIGF-I/rhIGFBP-3 combination. rhIGF-I has an inotropic effect that results in asymptomatic tachycardia in all treated patients, which disappears after several months of continued use (74).

Intracranial hypertension or papilledema occurs in approximately 5% of rhIGF-treated subjects. Headache is a frequent observation, but one placebo-controlled study found no difference in frequency of headaches between those receiving rhIGF-I or placebo injections (72). Lymphoid tissue hypertrophy associated with hypoacusis and snoring occurs in approximately 22% of patients. Tonsillar/adenoidal hypertrophy requiring tonsillectomy/adenoidectomy was seen in more than 10% of patients. Thirty-five percent of subjects having regular chest radiographs showed thymic enlargement (57). It is possible that some side effects may be more frequent than presently reported because they take time to develop. For example, the incidence of snoring was only 4% in the first year for the 25 longest-treated subjects in the study by Chernausek *et al.* (57) but increased to 65% for the entire study period. Parotid swelling and facial nerve palsy have also been described.

Anti-IGF-I antibodies develop in approximately half of the rhIGF-I-treated patients during the first year, but have no effect on response (57, 74). Transient elevation of liver enzymes has also been noted (74).

Acromegaloid coarsening of the face has been reported in a number of patients, particularly those of pubertal age (57). Body mass index increased from +0.6 SDS to +1.8 SDS during 4–7 yr of treatment with rhIGF-I in the European multicenter trial, and severe obesity occasionally occurred (55). However, body mass index measurement may not accurately reflect the degree of obesity in these children, and a doubling and even tripling of body fat (as demonstrated by dual energy x-ray absorptiometry) has been reported in children with GHI treated with rhIGF-I (75). In addition, hyperandrogenism with oligomenorrhea or amenorrhea, acne, and elevated serum androgens have been described in young adult patients given single daily injections of rhIGF-I (76). Although the long-term mitogenic effects of extended therapy with rhIGF-I in growing children is unknown, the evidence for a role for IGF-I in neoplasias (due to its mitogenic and antiapoptotic effects), increased cancer risk with hypersomatotropism, and evidence for aberrant tissue effects in rhIGF-I-treated patients dictate caution and a need for long-term follow-up of rhIGF-I-treated patients (77, 78). However, IGF-I replacement to normalize IGF-I levels rather than cause an elevation of IGF-I should not be associated with an increased risk for neoplasia.

Safety data of rhIGF-I treatment in children with height and serum IGF-I levels more than 2 SDS below the mean and peak GH above 7 ng/ml were presented as a poster in the 2007 meeting of The Endocrine Society. Eighty-six subjects meeting these criteria were treated for an average of 8 months. Adverse events included two cases of intracranial hypertension and one case of gastroenteritis and dehydration. Symptoms of hypoglycemia occurred in eight subjects (one of whom belonged to the control/observation group). Other reported adverse events were headaches, arthralgia, hypoacusis, gynecomastia, and snoring (79).

Indications for rhIGF-I Treatment

The FDA approval for the use of rhIGF-I reads as follows (from the rhIGF-I label): "rhIGF-I is indicated for the long-term treatment of growth failure in children with severe primary IGF-I deficiency and in children with GH gene deletions who have developed neutralizing antibodies to GH. Severe primary IGF-I deficiency is defined by a height SD score less than −3.0 and a basal IGF-I SD score less than −3.0 and normal or elevated growth hormone (GH). Severe primary IGF-I deficiency includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-I gene defects. These patients are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment. rhIGF-I is not intended for use in subjects with secondary forms of IGF-I deficiency, such as GHD, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of antiinflammatory steroids. Thyroid and nutritional deficiencies should be corrected before initiating rhIGF-I treatment. rhIGF-I is not a substitute for GH treatment."

The EMEA approved rhIGF-I "for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor I deficiency (primary IGFD). Severe primary IGFD is defined by: 1) height SD score <-3.0; 2) basal IGF-I levels below the 2.5th percentile for age and gender; 3) GH sufficiency; and 4) exclusion of secondary forms of IGF I deficiency, such as malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of antiinflammatory steroids. Severe primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-I gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment. It is recommended to confirm the diagnosis by conducting an IGF-1 generation test."

Following these recommendations, it is important to rule out other conditions such as malnutrition that are known to be associated with short stature, low serum IGF-I, and high GH levels before initiating therapy with rhIGF-I.

There are other hypothetical uses for rhIGF-I. These include conditions of IGF-I deficiency and poor growth such as chronic renal failure and prolonged failure to thrive. These conditions are associated with an acquired resistance to GH effects and high GH levels. Another group that should be investigated is children considered GHD who have a suboptimal response to rhGH use over at least a year, as assessed by lack of increment in growth velocity and lack of IGF-I response. As is the case in ISS, carefully controlled prospective studies are necessary to determine the benefits of optimizing IGF-I levels in such situations by administration of rhIGF-I.

Although not routinely used, the IGF-I generation test may prove to be a useful tool in differentiating GH unresponsive conditions from conditions that are responsive or partially responsive to GH. However, problems with the IGF-I generation tests, pointed out previously, need to be addressed and the methodology and criteria used for diagnosis need to be standardized. It is also important to determine whether rhIGF-I is superior to rhGH in conditions in which similar IGF-I concentrations are

achieved using either therapy. The role of combined use of rhGH and rhIGF-I needs to be further explored.

One important aspect of prescribing these therapies is cost [around $70.00 (U.S.) per kilogram of body weight of the patient per month of treatment, ranging from $50.00 to $90.00 (U.S.)]. Presently rhGH and rhIGF-I have near similar costs considering monthly dosages, with an approximate variation of 10%.

Conclusion

The availability of rhIGF-I alone for prescription adds to the arsenal of possible therapies that pediatric endocrinologists have for treatment of children with short stature. rhIGF-I has been demonstrated to accelerate growth and increase adult height in a limited number of patients with rare conditions. Therapy with rhIGF-I is not a substitute for rhGH therapy, nor is it currently approved for the treatment of children with failure of height gain with rhGH therapy. The approved indications for use of this agent are for children with significant short stature (more than 3 SD below the mean), low serum IGF-I levels (more than 3 SD below the mean), normal to high serum levels of GH, and for children with GH gene deletions who have developed inactivating antibodies to rhGH. Additional indications are under investigation, and therapy should not be initiated for these indications until clinical trial data are available or as part of a clinical trial.

We are in need of a better classification of IGF-I deficiency (80, 81) and studies assessing the utility of the IGF-I and/or IGFBP-3 generation test as well as studies comparing the effects of rhGH *vs*. rhIGF-I or both on statural growth and adult height in ISS and other conditions of acquired resistance to GH. It is a step forward to have more therapeutic options for patients with short stature. We only need to be careful and prove scientifically the effectiveness and safety of this step. At this juncture, expansion of the use of rhIGF-I beyond the absolute indications has not met the tests of demonstrating greater increases in growth velocity and predicted adult height SDS, being more cost effective, or having fewer side effects than available therapies.

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