Recombinant Human Insulin-Like Growth Factor I (rhIGF-I) and rhIGF-I/rhIGF-Binding-Protein-3: New Growth Treatment Options?

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INSULIN-LIKE GROWTH FACTOR I (IGF-I) AND GROWTH

The growth effect that gives growth hormone (GH) its name is the result of GH stimulation of IGF-I production in the liver (endocrine IGF-I) and peripheral tissues, particularly bone and muscle (autocrine/paracrine IGF-I).[1] Hepatic IGF-I circulates almost entirely (>99%) bound to IGF-binding proteins (IGFBPs). The IGFBPs are a family of six structurally related proteins with a high affinity for binding IGF. The principal BP, IGFBP-3, which binds 75% to 90% of circulating IGF-I, is a large ternary complex consisting of IGFBP-3, acid labile subunit (ALS), and IGF molecules. ALS and IGFBP-3 are produced in the liver as a direct effect of GH. The ALS stabilizes the IGF–IGFBP-3 complex, reduces the passage of IGF-I to the extravascular compartment, and extends its half-life.[2] The remainder of bound IGF-I is mostly with IGFBP-1 and IGFBP-2. IGFBP-1 concentrations are controlled by nutritional status as reflected in insulin levels, with the highest IGFBP-1 concentrations found in the fasting, hypoinsulinemic state.[3] Similarly, circulating concentration of IGFBP-2 is under negative control by GH directly, independently of IGF-I, and is elevated with GH deficiency or resistance; the positive effect of IGF-I on IGFBP-2 results in further elevation when patients who are GH receptor deficient (GHRD, Laron syndrome) are treated with IGF-I.[1,3] The IGFBPs modulate IGF action by controlling storage and release of IGF-I in the circulation and influencing its binding to its receptor, facilitating storage of IGF-I in extracellular matrices, and they also exert independent actions.[3]

IGF-I binds to the type 1 IGF receptor with high affinity and to the structurally similar insulin receptor with an affinity that is approximately 100-fold less that of insulin. Because IGF-I is present in the circulation at molar concentrations that are 1000 times those of insulin, even a small insulin-like effect of IGF-I as a result of its binding to the insulin receptor could be more important than that of insulin itself, were it not for the IGFBPs that control the availability and activity of IGF-I, and adapt to changing energy status.[3]

The importance of IGF-I in normal intrauterine growth in humans has been demonstrated in a patient with a homozygous partial deletion of the IGF-I gene,[4] in a patient with mutation of the IGF-I gene resulting in high circulating levels of an ineffective IGF-I,[5] and in patients with mutations of the IGF-I receptor,[6,7] who all had severe intrauterine growth retardation. Intrauterine IGF-I synthesis, however, does not appear to be GH dependent because most patients with genetically determined severe IGF-I deficiency have normal or only minimally reduced intrauterine growth. Standard deviation score (SDS) for length declines rapidly after birth in these conditions, demonstrating the immediate need for GH-stimulated IGF-I synthesis for postnatal growth.[1] Growth velocity in the absence of GH is typically half normal, but it has been reported to be normal or supranormal despite absence of GH in some hypothalamic conditions characterized by hyperphagia, with obesity or rapid weight gain.[8] A similar phenomenon was described in a placebo-controlled study of rhIGF-I treatment of patients with severe IGF-I deficiency from GHRD, in which 3 of the 9 placebo-treated subjects grew over the 6-month study period at an accelerated rate comparable with that of the rhIGF-I–treated subjects, attributed to improved nutrition in the investigative milieu.[9]

RECOMBINANT IGF-I (rhIGF-I) and rhIGF-I/rhIGFBP-3

Human IGF-I was synthesized by recombinant DNA techniques in 1986, and preparations of rhIGF-I for subcutaneous injection became available in 1990. The initial manufacturers in Japan (Fujisawa) and Sweden (Kabi) provided rhIGF-I for approximately 70 children with GHRD internationally and a handful of GH gene deletion patients with acquired GH insensitivity as a result of GH inactivating antibodies devel-

ALS	Acid labile subunit	IGF-I	Insulin-like growth factor I
GH	Growth hormone	rhIGF-I	Recombinant IGF-I
GHD	GH deficient	SDS	Standard deviation score
GHRD	GH receptor deficient	FDA	US Food and Drug Administration
IGFBP	IGF-binding proteins		

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Table. Known abnormalities affecting the growth hormone (GH) insulin-like growth factor I (IGF-I) axis resulting in IGF-I deficiency

1. Mutations resulting in isolated GH deficiency (IGHD) or multiple pituitary hormone deficiency (MPHD)
   - Pituitary differentiation factors [HESX1, LHX3, LHX4, SOX3, GLI2, PITX2, PROP1, PIT1 (POU1F1)]
   - GH-releasing hormone receptor
   - GH-1 gene
2. Other causes of IGHD, MPHD, congenital (eg, Prader-Willi syndrome, septo-optic dysplasia) and acquired (radiation, tumor, hypophysitis, central nervous system infection)
3. Acquired GH-inhibiting antibodies
4. GH receptor deficiency
5. GH-GH receptor signal transduction factor mutation (Stat 5b)
6. IGF-I gene mutations
7. Acid labile subunit (ALS) mutation

Note: Catabolic states and chronic illness may have effects on GH secretion, GH receptor sensitivity, IGF-I synthesis, or IGF-binding proteins.

oping after treatment with rhGH. The drug was also used for treatment of insulin resistance states,[10] and a US manufacturer (Genentech, South San Francisco, Calif) began recruitment for a study using rhIGF-I as adjunctive therapy in diabetes; the study was aborted "based on the scope and extended timeframe of the clinical program that would be required to address potential concerns about diabetic retinopathy when using IGF-I in Type I and Type II diabetes mellitus."[11]

Eventually, the three manufacturers stopped production of rhIGF-I because of the limited applicability. Subsequently, a company licensed by the US manufacturer (Tercica Inc., Brisbane, Calif) obtained approval of the drug (Increlex™, mecasermin) from the US Food and Drug Administration (FDA) in late 2005. Soon thereafter, an equimolar complex of IGF-I and IGFBP-3 (Iplex™, mecasermin rinfabate, Insmed Inc., Glen Allen, Va) was approved by the FDA. In addition to the purported pharmacokinetic advantage permitting once daily injection for the latter preparation, lower concentrations of free IGF-I were anticipated, with a lower risk for hypoglycemia than when rhIGF-I is injected without the binding proteins.[12] The commercial viability of these preparations in the broad growth market depends on the recognition of a substantial population that would derive specific benefits from such replacement therapy.

WHAT ARE THE CAUSES OF IGF-I DEFICIENCY?

The known causes of IGF-I deficiency are summarized in the Table. Those abnormalities that precede the GHR are readily treatable with rhGH, whereas IGF-I deficiency that is the result of GHR and GH-GHR signal transduction abnormalities, inactivating GH antibodies, or IGF-I gene mutations requires treatment with rhIGF-I. Patients with IGF-I type 1 receptor mutations are not IGF-I deficient and are not responsive to rhIGF-I.[6,7]

The approvals of mecasermin and mecasermin rinfabate by the FDA were for treatment of "severe primary IGF-I deficiency," which includes patients with defects in the GHR, and more rarely in the post-GHR signaling pathway or IGF-I gene, and for the also more rare GH unresponsiveness resulting from the development of inactivating antibodies in some GH gene deletion patients treated with rhGH.

HOW IS IGF-I DEFICIENCY DIAGNOSED?

"Severe primary IGF-I deficiency" was defined in the FDA approval statements by height SDS ≤ -3 with a basal IGF-I SDS also ≤ -3, and normal or elevated GH (method of testing not specified). Younger children may have quite low values for IGF-I that are not diagnostically useful, and normal ranges may vary as much as 15-fold, depending on the laboratory. The reliability of IGF-I assays also varies greatly; 3 out of 4 laboratories, using the above criterion, were unable to identify 15% to 20% of Ecuadorian patients with severe IGF-I deficiency from mutation of the GHR.[13] Spuriously low values may result from the high susceptibility of IGF-I to postsampling proteolysis.[14] Another variable in the assay of IGF-I is the fasting state, which can be associated with substantial reduction in IGF-I levels.[15] As noted above, a variety of nonhormonal conditions can be associated with suppressed IGF-I, including idiopathic short stature.[16]

WHAT IS THE EXPERIENCE OF TREATMENT WITH rhIGF-I?

Published Experience

Published reports include approximately 60 children with GHRD or GH inactivating antibodies who have been treated for 2 years or longer with rhIGF-I injections. With the exception of nine patients treated in Israel with 150 μg/kg injected once daily,[17] treatment has usually been with dosages varying from 80 to 120 μg/kg twice daily.[18-20] Growth responses have been a doubling or tripling of baseline velocities of 3 to 4 cm/year in the first year, decreasing considerably in the second year. Height SDS increases over 2 years are 1.2 to 1.5 with two thirds of the improvement occurring in the first year.[17-20] Comparison of growth response of 22 rhIGF-I–treated GHRD patients with 11 GH-treated GH deficient (GHD) patients in the same setting and with comparable growth failure demonstrated growth velocity increment in those with GHRD to be 63% of that achieved with GH treatment of GHD in the first year and $<50\%$ in the second and third years.[18] The report from the European study described 17 patients treated for 48 months or longer. Overall increase in height SDS was 1.67 ± 1.16, suggesting modest continued improvement over time in this group but still markedly less than expected with GH replacement therapy.[20] Among 8 patients treated for more than 6 years, the mean height SDS improved from -5.6 to -4.5 in the second year, -4.4 in the fourth year, and -4.2 in year 6, again emphasizing modest, at best, acceleration far different than that seen with long-term GH treatment of GHD. The lesser response