Introduction of New Recombinant Insulin-like Growth Factor-1 – Current and Future Perspectives

a report by

Michael B Ranke

Professor of Paediatrics, and Head, Section of Paediatric Endocrinology, University of Tübingen Children's Hospital

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The past 50 years have seen extraordinary developments, from the somatomedin hypothesis[1] to a broad understanding of the insulin-like growth factor (IGF) system with its varied components and diverse actions.[2] At the centre of the system is IGF-1, the insulin-like peptide with major effects on metabolism and cellular function. The fundamental physiological effects of IGF-1 on glucose metabolism and growth were discovered in the 1980s,[3,4] when it was proved that the most important similarities between insulin and IGF-1 involved their metabolic effects on cellular glucose, amino acid uptake, glycogen synthesis, lipogenesis and mitogenesis. In 1983, the cloning of recombinant human IGF-1 (rhIGF-1) laid the foundation for the production of sufficient amounts of recombinant material for clinical use.[5] The resulting industrial production enabled the exploration of this new drug within the framework of clinical trials involving various disorders. The main focus in the 1990s was the investigation of the growth-promoting and insulin effects of IGF-1, while current experimental and clinical trials deal with the neuroprotective potential of IGF-1.[6–9] Clinical studies were brought to an abrupt halt in the 1990s owing to suggestions in cohort studies of an association between high levels of IGF-1 and malignancies.[10] Consequently, on the grounds of risk–benefit assessments and economic considerations, manufacturers of IGF-1 decided to discontinue their involvement in clinical research. This negative outlook changed after expanding knowledge in the field led to a rational re-assessment of the therapeutic potential of IGF-1 (see *Table 1*). More recently, rhIGF-1 (Increlex®) received marketing authorisation in the US in 2006, and in 2007 the EU approved IGF-1 in the treatment of severe primary IGF deficiency.

This brief article aims at summarising clinical experience with regard to the efficacy and safety of IGF-1, focusing on the role of IGF-1 in the treatment of growth disorders, diabetes and insulin resistance, as these diagnoses serve as the empirical basis for the knowledge we have gained.

The Insulin-like Growth Factor–Growth Hormone System

In 1957, Salmon and Daughaday found proof of a growth hormone (GH)-dependent factor that had a growth-promoting effect on epiphyseal cartilage. They called it the 'sulphation factor' owing to its mediation of sulphate. Subsequently, the more general term 'somatomedin' was proposed[1] in view of the diverse metabolic effects of this factor and its insulin-like nature. Somatomedin was found to have two proteins, which due to their structural resemblance to insulin were termed 'insulin-like growth factors' (IGF-1 and IGF-2).[11,12] Through binding studies and molecular investigations it became evident that there were specific cell membrane (type 2 kinase) receptors: IGF-1-R and IGF-2-R. It is possible for both IGF-1 and IGF-2 to bind with the insulin receptor; the binding affinity of IGF-1 with the insulin receptor represents only one-hundredth that of insulin.[13] The 'insulin-like' effects of the IGFs are thus related to the cellular uptake of glucose and amino acids, glycogen synthesis, lipogenesis and mitogenesis.[14,15] Specific effects include their function in cell differentiation, cell proliferation and apoptosis. The complexity of the IGF system is enhanced by the fact that certain proteins specifically bind IGFs; these proteins are known as 'IGF-binding proteins' (IGFBP-1–6).[16] Although structurally similar, these proteins can be modified individually by phosphorylation, glycosylation and proteolysis, and this in turn can affect their ability to bind IGFs. IGFs and IGFBPs can be expressed in almost every type of tissue.[17] The IGFs and IGFBPs found in the blood circulation are mainly synthesised in the liver. The secretion of GH, insulin and sex steroids, liver function and nutritional status are major determinants of circulating levels of IGFs and IGFBPs.[18] The degradation of IGF is impeded through association with binding proteins and the acid-labile subunit (ALS), and its half-life is prolonged by hours.[19,20] Only about 1–2% of IGF-1 in the circulation is 'free' (according to the law of mass action). IGF in the circulation is transported to various peripheral target organs through binding protein cascades. Thus, several biological functions can be attributed to IGFBPs.[17]

GH is a peptide hormone expressed in a pulsatile way in the somatotrope cells of the anterior pituitary.[21] The growth-promoting effect of GH occurs either indirectly, via the stimulation of IGF-1 in the liver, or directly, on the epiphyseal growth plate or by means of IGF-independent effects. GH stimulates the expression of IGF-1, IGFBP-3 and ALS in the liver; these then reach the epiphyseal plate through the blood circulation. GH in the epiphyseal plate stimulates the expression of pre-chondrocytes and the local synthesis of IGF-1.[22] GH and IGF-1 are both prerequisites for the optimal longitudinal growth of bones. IGF-1 and GH have a synergistic effect on growth and anabolic metabolism; they have an antagonistic effect on the metabolism of glucose and fat due to the anti-insulin effect of GH[23] and the insulin-like effect of IGF-1.[4]

Insulin-like Growth Factor-1 Deficiency

IGF-1 concentrations in the circulation and GH are quantitatively connected by means of a typical endocrine circuit.[24] When the secretion of GH is diminished (GH deficiency), equally low levels of the GH-

Michael B Ranke is a Professor of Paediatrics and Head of the Section of Paediatric Endocrinology at the University of Tübingen Children's Hospital. His primary clinical interests include growth (disease-specific growth), syndromes (e.g. Turner syndrome), insulin-like growth factors (IGFs), IGF-binding proteins (IGFBPs) (diagostic value, IGF therapy), growth hormone (outcomes research, prediction models, metabolic effects), standardisation of methodology (evidence-based medicine, hormone measurements, procedures) and epidemiology (diabete). His basic science interests include growth hormone (action, gene defects), IGFBP3/IGFBP2 (e.g. BP2 in malignancies) and growth genes (SHOX). Professor Ranke has been an elected Fellow of the Royal College of Physicians since 1992.

E: Michael.Ranke@med.uni-tuebingen.de

dependent IGFs (IGFBP-3, ALS) are found. In this situation, exogenous GH leads to the normalisation of IGF-1, IGFBP-3 and ALS, as well as to the stimulation of growth. If the synthesis of IGF-1 is diminished despite normal pituitary function, the result is a reduction of growth even though GH secretion is normal (or high). For example, this occurs in cases of GH receptor defects (Laron syndrome) or in defects of the intracellular JAK-STAT signal transduction cascade.[25,26] Pronounced short stature is found in these conditions, and the phenotype is similar to severe GH deficiency. Furthermore, a deficiency in circulating IGF-1 can be caused by conditions that affect the expression of IGF-1, such as malnutrition, hypothyreosis, renal insufficiency and liver insufficiency. In all cases of short stature associated with low concentrations of IGF-1 despite the fact that the pituitary is able to secrete sufficient GH, it is possible to compensate for diminished growth through IGF-1 therapy but not through exogenous GH. However, to date there is no uniformity in the nosological nomenclature relating to all of these situations.[27,28]

In the classic concept of endocrine regulatory systems – regulated hormones of the endocrine organs, e.g. thyroxine (T4) in the thyroid, and regulating hormones, e.g. thyroid-stimulating hormone (TSH) in the pituitary – primary disorders are generally understood to be those in which the endocrine organ is affected; in the case of the thyroid, T4 is low, therefore TSH is high. Secondary disorders are understood to be those in which the regulatory system is affected, e.g. in the pituitary TSH is low, therefore T4 is low. For example, the GH-IGF system can be considered as one in which IGF-1 is the regulated peripheral hormone. Therefore, a secondary deficiency entails low GH and, thus, low IGF-1, as opposed to a primary deficiency, which would entail low IGF-1 and, therefore, normal/high GH (see *Table 2*).[24] The approval for IGF-1, based on the above information and nomenclature, relates to a sub-group of short children with a primary deficiency, whereas the term secondary is related to cases in which the deficiency is not considered an expression of cellular disturbances of IGF-1 synthesis caused by GH (or related to an IGF-1 gene defect). In this context, the term secondary implies a reduction of IGF-1 synthesis, which can principally be eliminated by eliminating other disturbances, e.g. nutritional, thyroid, etc. However, in light of several molecular pathomechanisms, in this case it is not appropriate to define an endocrine disease exclusively on the basis of the effect of another hormone. Such an approach would imply that disturbances in the GH-IGF system can be reduced to descriptive terms such as 'GH-sensitive' and 'GH-insensitive'.

Evidence of a 'Severe' Primary Insulin-like Growth Factor-1 Deficiency

The EU's approval of IGF-1 therapy includes a defining limit for the severity of primary IGF-1 deficiency: height in relation to age (<-3.0 standard deviation score [SDS] = very short); and degree of IGF-1 concentration in the blood (<-2.5th percentile). In addition, an IGF-1 generation test is recommended to further confirm the diagnosis. This IGF-1 generation test is basically an investigation of short-term changes in IGF-1 blood concentrations following a dose of recombinant GH; such quantifications of IGF-1 concentrations can indicate the degree of GH sensitivity. In the test, the responsiveness to exogenous GH (usually over three to seven days) is examined in terms of of IGF-1 synthesis. It is assumed that these data reflect the improvement in growth during long-term GH treatment. In the identification of patients with GH resistance, Blum et al. suggested that levels of IGF-1 that remain <15µg/l and IGFBP-3 that remain <400µg/l in the test should be considered pathological. Changes in the plasma concentrations of IGF-1 were measured four days after a subcutaneous dose of GH of 33µg/kg/bodyweight (BW).[29,30] However, the literature relating to this test procedure makes it clear that the GH dose is not standardised, and neither is there uniformity in terms of time intervals or in the expected increase in levels of IGF-1 and IGFBP-3 among pre-pubertal and pubertal children.[31,32] Published reports also demonstrate that pathological results were found in other situations, such as GH deficiency, idiopathic short stature and Turner syndrome.[33,34] This implies that a small increase in IGF-1 is not exclusively indicative of a primary IGF-1 deficiency. Molecular genetic methods can also be employed in the verification of a gene defect in the GH receptor or in components of the post-receptor signal cascade.[35,36]

Table 1: Therapeutic Potential of Insulin-like Growth Factor-1

Systemic applications
Growth disorders
Severe primary IGF deficiency, e.g. Laron syndrome
Diminished effect of GH, disturbances in the signal paths of JAK/STAT, e.g. chronic renal insufficiency, wasting syndrome, idiopathic short stature
Insulin resistance
Severe congenital insulin resistance syndromes, e.g. leprechaunism, insulin receptor defects
Type 1 diabetes (associated with complex cases)
Type 2 diabetes (associated with complex cases)
Neuroprotection
Following hypoxic insult (putative)
Neurodegenerative disorders, e.g. amyotrophic lateral sclerosis
Local applications
Wound-healing disorders
Tissue reconstruction and repair
Extracorporeal tissue growth

GH = growth hormone; IGF = insulin-like growth factor.

Treatment of Short Stature and Primary Insulin-like Growth Factor-1 Deficiency

The use of rhIGF-1 for treating short stature caused by a severe primary IGF-1 deficiency began in the early 1990s. The clinical picture was described by Laron as a GH receptor defect, and involved a broad phenocopy of severe GH deficiency, normal GH secretion and GH resistance.[37] The availability of rhIGF-1 led to these patients being treated, along with a few other patients with classic GH deficiency who developed neutralising GH antibodies during therapy with mainly extractive GH. Laron and colleagues were also the first to report the results of the treatment of five children with Laron syndrome. Ages ranged from 3.3 to 14.5 years, and the daily dose of rhIGF-1 was 150µg/kg/BW delivered subcutaneously. An increase in growth velocity was observed in the first year of treatment, from 2.8–5.8 to 8.8–13.6cm/year. Long-term experience with rhIGF-1 therapy has been reported by four main study groups: in Israel,[37,38] Ecuador,[39] Europe[30,40,41] and the US.[42–44] A total of 150 children and adolescents were treated with rhIGF-1 produced by different manufacturers. Two daily doses were given in the studies, except in the Israeli study in which rhIGF-1 was injected only once daily. The results demonstrate a remarkably homogenous effect on long- and short-term growth. This is particularly noteworthy in view of the heterogeneity of patients in terms of ethnic origin, geographical location or manufacturer's brand (see *Table 3*). Short-term investigations[39] have shown a positive correlation between dosage and growth rate. Longitudinal studies[41,42] provide evidence for a substantial improvement in height. However, the final height results for GH treatment in GH-deficient patients have proved to be better than those in studies of IGF-1 treatment of severe primary IGF-1-deficient patients. The reasons for this are: the absence of direct GH effects on the epiphyseal growth plate; the fact that GH fails to stimulate the local

Table 2: Classification of the Causes of Insulin-like Growth Factor-1 Deficiency

	Secondary IGF-1 Deficiency	Primary IGF-1 Deficiency	Primary IGF-1 Deficiency	Functional IGF-1 Deficiency
Pathogenesis	Defects in GH production	Defects in GH action	Defects in IGF production	Defects in IGF action
GH secretion	Low	High/normal	High/normal	High/normal
Level of disorder	GH production: • GHRH/GHRIH defects • GHRHR defects • GH gene defects • Functional (ageing) • Other	Binding with GHR: • Anti-GH ABs • GHBP excess	IGF-1 gene: • Mutation/deletion • Other	Binding protein deficiency • IGFBP-3 • ALS • Other
Level of disorder	Development of the pituitary • Cell structures • Other	GH receptor • GHR ABs • GHR gene defects	Co-factors • Thyroid hormones • Insulin • Nutrition • Liver function • Other	Excess binding proteins • IGF-1 ABs • Renal insufficiency • Other
Level of disorder	Destruction of the pituitary	Post-GHR • JAK/STAT • Other		IGF-1 receptor • IGF-1-R • Post-receptor

ABs = antibodies; GH = growth hormone; GHR = growth hormone receptor; IGF = insulin-like growth factor.
Source: Ranke, 2006.[24]

Table 3: Growth During Insulin-like Growth factor-1 Therapy in Various Studies

Studies	n	Age (years)	Height (SDS)	Dosage rhIGF-1 (µg/kg BW)	Growth Rate First Year (cm/year)	Height (SDS) at Therapy End
First year						
Klinger and Laron[38]	9	7.4	-5.7	150–200; 1x	8.2	
Backeljauw et al.[42]	8	6.6	-5.6	80–120; 2x	9.3	
Ranke et al.[40]	26	8.2	-6.5	40–120; 2x	8.5	
Guevara et al.[68]	22	9.1	-8.4	80–120; 2x	8.9	
Chernausek et al.[44]	59	7.8	-6.5	40–120; 2x	8.0	
Long-term						
Ranke et al.[41]	17	9.1	-6.5	40–120; 2x	4 years	-4.8
Chernausek et al.[44]	6	9.9	-7.3	40–120; 2x	7 years (adult)	-4.8

BW = bodyweight; rhIGF-1 = recombinant human insulin-like growth factor 1; SDS = standard deviation score.

expression of IGF-1 in epiphyseal chondrocytes; the fact that rhIGF-1 cannot normalise IGFBP-3 and ALS, thus leading to rapid degradation of circulating IGF-1; and dosage problems in which higher (adequate) doses are associated with the risk of hypoglycaemia (see below). Few reports are available about the therapy-related changes occurring in other tissues and organs. Laron and Klinger[38] described a reduction in fat tissue after 12 months of therapy. We and other groups[41,45] observed a moderate increase in fat mass during long-term therapy. Chernausek et al.[44] studied bone age as well as changes in the size of the kidneys and spleen; however, their results did not show an overproportionally high acceleration of bone age, and neither was there an alteration in organ size.

Adverse Effects

A series of typical adverse events are associated with IGF-1 therapy.[39,40,44] These can be categorised as follows: metabolic (hypoglycaemia); induction of growth in lymphatic tissue; and other effects (see *Table 4*). Children with primary and secondary IGF-1 deficiency tend *a priori* to suffer from hypoglycaemia. This risk is lower in GH-deficient children treated with exogenous GH, whereas in those treated with IGF-1 therapy the risk is probably high. This situation is associated with the genuine insulin-like effects of IGF-1, through which the peripheral uptake of glucose is augmented and the production of hepatic glucose is lowered, as well as with the insulin-sensitising attributes of IGF-1. From the statistical perspective, the study by Chernausek et al.[44] showed that glucose concentrations <50mg/dl were not more frequently observed under IGF-1 therapy than in therapies not involving IGF-1. Nevertheless, hypoglycaemia occurred in 49% of patients under IGF-1 therapy, four of whom suffered seizures. European studies showed that hypoglycaemia was avoidable when the injection was preceded by a meal. Headaches, benign intracranial hypertension and papilla oedema result from the IGF-1-mediated effects (at least initially) of fluid retention. The augmentation of lymphatic tissue growth (tonsils, adenoids, spleen, thymus) is a characteristic side effect of IGF-1 and GH. Anti-IGF-1 antibodies were found in approximately half of patients,[44] in low titrations; however, no physiological significance could be attached to the findings. A coarsening of facial features, especially during puberty, was observed in isolated cases.[30]

Diabetes and Insulin Resistance

An impairment in the action of insulin is the result of a variety of congenital and acquired disorders[46] (see *Table 1*). Severe impairments in insulin sensitivity result from the inhibition of insulin action or impaired signal transduction at the cellular level.[23,47–49] Impaired insulin action resulting from high-capacity, high-affinity insulin antibodies is rare. The cause of insulin resistance in patients with obesity, hyperandrogenism and acanthosis nigricans is attributable to anti-insulin receptor autoantibodies. Other states of insulin resistance, such as the Rabson-Mendenhall syndrome, are caused by mutations of the insulin receptor.[50] There are a multitude of complex clinical syndromes associated with

profound insulin resistance whose pathogenesis is still poorly understood. According to our current understanding of type 2 diabetes, the disease is caused by a combination of insulin resistance and an insulin secretion disorder. An increase in hepatic gluconeogenesis (hepatic insulin resistance) and an impaired glucose uptake by skeletal muscle (peripheral insulin resistance) are considered to be the coinciding pathogenetic mechanisms, and involve both genetic predisposition as well as acquired components. Hyperglycaemia, hyperinsulinism and insulin resistance, together with dyslipidaemia, are associated with vascular disease in type 2 diabetes.[47] In insulin-dependent diabetes, impaired sensitivity is related to the developmental changes occurring during puberty or pregnancy, for instance, or to other factors such as obesity or poor metabolic control. The most important hormonal and metabolic antagonists of insulin action are GH and free fatty acids, as well as triglycerides. In badly controlled insulin-dependent diabetes, GH secretion is elevated due to a moderate impairment of IGF-1 levels.[48,49] Recent investigations with liver IGF-1-deficient mice[23] have confirmed that impaired insulin sensitivity in IGF-1-deficient animals is the direct result of an excess of GH.

In 1987, Guler, Zapf and Froesch[3] compared the short-term metabolic effects of 100µg/kg/BW IGF-1 with those of 0.15IU/kg/BW insulin, which was given intravenously to eight healthy volunteers. They observed that both substances led to nearly identical hypoglycaemic effects. On a molar basis, the potency of IGF-1 was only one-twentieth that of insulin. Investigations by Turkalj et al.[51] in which rhIGF-1 was infused at dosages ranging from 5 to 30µg/kg/BW/hour in healthy adults showed dose-dependent effects on variables such as glucose, lipid and amino acid metabolism, which were similar to those produced by insulin but with evidence of diminished endogenous insulin secretion. Although the hypoglycaemic effects of corresponding doses of insulin and rhIGF-1 were found to be similar, Laager and Keller[52] observed that the counter-regulatory increases in glucagon, adrenalin, cortisol and GH were less intense after IGF-1 administration. Cusi and DeFronzo[53] recently used a euglycemic insulin clamp to analyse the response to seven days of rhIGF-1 (80µg/kg subcutaneously twice daily) in eight patients with severe type 2 diabetes. Their results showed that glucose and insulin levels and endogenous glucose production decreased after IGF-1 infusion, but the underlying abnormality involving hepatic and muscular insensitivity to insulin did not completely normalise. As a consequence of such experimental studies, clinical trials were conducted to study patients with severe insulin-resistant states[54–58] and/or type 2 diabetes.[59–61] In most of these investigations, rhIGF-1 was applied for less than three months at dose levels of 50–100–160µg/kg/BW, injected subcutaneously once or twice daily. However, the results of a trial of patients with severe insulin resistance who were treated for up to 12 months suggested that IGF-1 may be an efficacious and safe long-term therapy in situations in which other alternatives are not yet available.[62] The majority of the investigators expressed a positive opinion regarding the efficacy of rhIGF-1 in terms of the metabolic control of the patients treated. In children[48] and adults[49,63] with type 1 diabetes, rhGH has also been used as an adjunct to improve metabolic control, with glycaemic control improving with a concurrently lower demand for insulin and a reduction of GH secretion. However, no long-term studies of these diabetic states have been conducted. In addition, a striking number of adult patients complained of side effects such as oedema on the face and hands, mild weight gain, jaw tenderness, arthralgias, myalgias and tachycardia.[59] Many of the investigators regarded these side effects as unacceptable, despite the beneficial effects of rhIGF-1 on glucose and lipid metabolism.[64]

Table 4: Side Effects of Insulin-like Growth Factor-1 Therapy in Various Studies

	Ranke et al.[40]	Guevara et al.[39]		Chernausek et al.[44]
		Placebo	IGF-1	
	n=33	n=9	n=7	n=76
Hypoglycaemia	13 (39%)	6 (67%)	6 (87%)	37 (49%)
Hypertrophy of tonsils/adenoids				17 (22%)
Tonsilectomy/ adenotomy	2 (9%)			17 (22%)
Thymus hypertrophy				8 (35%)
Sleep apnoea				3 (4%)
Lipohypertrophy at the injection site	7 (21%)			24 (32%)
Headache	21 (64%)	2 (22%)	2 (29%)	
Pain at the injection site	16 (48%)	3 (33%)	3 (43%)	

IGF = insulin-like growth factor.

Discussion

In children with the rare diagnosis of severe primary IGF-1 deficiency, IGF-1 replacement therapy is the pathophysiologically correct form of treatment; currently, no other alternative forms of treatment are available.[65] The significance of such a therapy can be deduced from the fact that final height in untreated patients is around 130cm. The pathophysiological complexity of severe primary IGF-1 deficiency also involves the influence of other GH-dependent components in the IGF system that could be relevant to the effectiveness of circulating IGFs in the target organ. Thus, IGF-1 replacement alone cannot lead to their normalisation. Neither IGFBP-3 nor ALS is available in therapeutic form, thus IGF-1 represents the only possible therapy to date. The risk of hypoglycaemia after an IGF-1 injection is, on the one hand, intrinsic; on the other hand, however, it is associated with the dosage, age and individual reaction of the patient. The treatment has been proved to be very safe, even in patients who have been treated over several years. Due to its complexity, IGF-1 therapy belongs in the specialised hands of experienced paediatric endocrinologists and diabetologists. Since this is a novel type of therapy, observational studies including documentation are essential. Modifications in dosage should, in our opinion, be carried out in a stepwise manner, and should involve accurate tests of metabolism. Since the potential influence of IGF-1 is manifold and extends beyond its effects on growth, it is crucial that treatment be accompanied by tests aimed at differentiating the various changes in function and composition of the body. In light of the diverse potential of IGF-1 treatment (see *Table 1*), it can be assumed that it will continue to be applied in a similar manner in terms of dosage and form of application (e.g. depot), in combination with other therapy forms (e.g. with IGFBPs and/or GH) as well as in new approaches in drug targeting. This form of therapy will continue to be discussed in the context of the role of growth factors in the manifestation of malignant disease.[66,67]

In addition, IGF-1 (alone or in conjunction with insulin) has been shown to improve metabolic control among patients with type 1 diabetes whose disease is poorly controlled through conventional means. However, the long-term potential of IGF-1 treatment in these situations has not yet been explored. One explanation for this is the fact that inappropriately high IGF-1 levels are associated with certain malignancies in adults.[10] New therapeutic principles aimed at improving insulin sensitivity are currently being explored. The therapeutic potential of IGF-1 in growth disorders,

diabetes and insulin resistance has yet to be explored fully. Dosages, modes of application (e.g. slow-release forms) and combinations with binding protein(s) and GH need to be studied extensively in the future with regard to the conditions outlined in *Table 1*. ■

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