Mecasermin rinfabate for severe insulin-like growth factor-I deficiency

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Recombinant human insulin-like growth factor (rhIGF)-I has been shown to increase growth velocity in children with IGF-I deficiency, either as a result of growth hormone-insensitivity syndrome or IGF-I gene deletion (one case study). There have been adverse events, particularly hypoglycemia, reported with administration of unbound rhIGF-I. In addition, the serum half-life of unbound rhIGF-I is shorter when administered to patients with growth hormone-insensitivity syndrome, who have low serum concentrations of its binding proteins IGFBP-3 and acid-labile subunit, than when administered to normal volunteers or to patients with an IGF-I gene deletion (who had normal levels of IGFBP-3). Mecasermin rinfabate, an equimolar mixture of rhIGF-I and the recombinant form of its principal binding protein rhIGFBP-3 (rhIGF-I/rhIGFBP-3), was developed to prolong the half-life and to reduce the risk of acute adverse events (particularly hypoglycemia) associated with administration of rhIGF-I. Published data demonstrate the efficacy of mecasermin rinfabate in treating severe primary IGF-I deficiency, and mecasermin rinfabate appears to have a longer half-life in patients with growth hormone-insensitivity syndrome than unbound rhIGF-I.

Keywords: growth hormone, growth hormone insensitivity syndrome, hypoglycemia, IGFBP-3, IGF-I, insulin-like growth factors, Laron syndrome

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Growth hormone-insensitivity syndrome (GHIS) is characterized by a failure to synthesize insulin-like growth factor (IGF)-I in spite of normal or elevated levels of growth hormone (GH) [1]. One of the causes is GH receptor defect, or deficiency (GHRD, Laron syndrome), a rare autosomal recessive condition first described in 1966 [2] and recently reviewed [3], and there have been a variety of different mutations described that account for this condition [4], most involving mutations in the extracellular domain of the GH receptor. GHRD is characterized by growth failure starting in infancy that is unresponsive to GH administration, associated with normal or elevated levels of GH and decreased levels of IGF-I and IGF binding protein (IGFBP)-3 [5–7]. There has also been a patient described with a similar presentation who has a deletion of the gene for IGF-I [8]. Another cause of GHIS arises in patients with GH gene deletion, in whom neutralizing antibodies develop when treated with recombinant human GH (rhGH). These conditions are collectively known as severe primary IGF-I deficiency and are very rare; approximately 250 cases of Laron syndrome have been described worldwide. It may be that partial IGF-I deficiency (or partial GHIS) could account for some cases of idiopathic short stature (i.e., children with growth failure), who do not have GH deficiency and who do not have any other explanation of their growth failure [9]. To date, there have been no studies reported that have evaluated treatment of idiopathic short stature with IGF-I.

Overview of the market

There are currently two compounds available for the treatment for growth disorders in which GH is ineffective owing to GH resistance, or where there is a *GH* gene deletion leading to rapid neutralizing antibody formation after treatment with GH. Both of these compounds have IGF-I as the major active component. The first component, mecasermin, which is rhIGF-I alone (Increlex™, Tercica, Inc., CA, USA), received approval from the US FDA in August 2005. The second compound is mecasermin rinfabate (IPLEX™ [formerly known as SomatoKine], Insmed Inc., VA, USA), which was similarly approved in December 2005. It is a complex of equimolar amounts of rhIGF-I and its most abundant binding protein, rhIGFBP-3. The complex was developed in order to increase the half-life of rhIGF-I and to decrease the risk and/or severity of acute adverse events (particularly hypoglycemia) associated with administration of rhIGF-I.

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Introduction to mecasermin rinfabate

Chemistry

Normal growth is a complex, multifactorial process and involves both endocrine and nonendocrine processes. Factors contributing to the growth process include genetic factors, endocrine factors (GH and the nonpeptide hormones thyroxine, androgens, estrogens and glucocorticoids), as well as environmental factors, such as nutrition, stress and sleep [10]. GH plays a major role in normal growth. It is a peptide secreted by the pituitary gland under the positive control of GH-releasing factor (GHRH) and the negative control of somatostatin. GH acts by binding a GH receptor. GH circulates bound to a binding protein, which is the extracellular portion of the GH receptor [11]. When GH binds to two GH receptors, an intracellular cascade takes place involving the activate Janus kinases signal transducers and activators of transcription (JAK-STAT) signaling system, which results in production of IGF-I, the agent thought to carry out most of the actions of GH related to growth at the growth plate.

IGF-I and -II are small peptide hormones (~7.5 kD) that share a high degree of homology with proinsulin [12–14]. IGFs are produced almost ubiquitously and circulate at high concentrations in serum. As with insulin, they possess the ability to increase glucose disposal. Beyond their insulin-like effects, these growth-promoting peptides influence cellular proliferation and differentiation in numerous tissues [15]. For IGFs to exert their effects at the cell surface, they first must bind specific, high-affinity cell-surface receptors, principally the type I IGF receptor. However, the interaction of IGFs with cell surface receptors is tightly regulated by at least six distinct high-affinity carrier proteins, the IGFBPs and possibly by several low-affinity IGFBP-like molecules [16]. IGFBPs 1–6, which are present in serum and many biologic fluids, have similar or higher affinities for IGF-I and -II than the type I IGF receptor. Therefore, the interaction of IGFs with IGFBPs can prevent untoward IGF effects, such as uncontrolled cellular proliferation or hypoglycemia. Conversely, disruption of the IGF–IGFBP complex is a probable prerequisite for IGFs to exert their mitogenic and metabolic effects through the IGF receptor. Specific proteases have been described that hydrolyze IGF binding proteins, which may regulate IGF-I activity [17]. The major source of circulating IGF-I is the liver; IGF-I circulates in serum as part of a 140-kDa complex consisting of equimolar amounts of IGF-I, IGFBP-3 and a third factor known as acid-labile subunit (ALS) [15]. It has been demonstrated that IGFBPs possess IGF-independent metabolic effects that may counterbalance those of IGF-I (e.g., antiproliferative) [18]. A recent review suggests that these IGF-independent effects may include inhibition of growth, antagonizing insulin action and inhibiting the progression of malignant tumor growth in transgenic mice by promoting apoptosis of cancer cells [19].

Pharmacodynamics

IGF-I elicits most of its physiological effects through a specific cell surface receptor, the type I IGF receptor, though it is also capable of binding to the insulin receptor. Although IGF-I can induce insulin-like effects, its predominant effect is to promote cell division, growth and differentiation of many cell types. Bound IGF-I is biologically inactive.

Phase I studies: pharmacokinetics & metabolism

The half-life of the IGF-I–IGFBP-3–ALS ternary complex has been reported to be longer than 12 h [20,21]. In a patient with a partial *IGF-I* gene deletion (in which there are normal IGFBP-3 levels), a single subcutaneous injection of rhIGF-I (40 or 80 µg/kg) resulted in half-lives of elimination of 15.7 and 14.3 h, respectively, and maximum IGF-I levels of 341 and 794 µg/l, respectively [22]. Grahnén and colleagues studied the pharmacokinetics of subcutaneously injected rhIGF-I in healthy volunteers and patients with GH receptor deficiency [23]. In healthy volunteers, the maximum concentration was achieved at approximately 7 h. Following daily multiple injections of 40 µg/kg, IGF-I levels increased by 277 µg/l above baseline. Clearance and half-life was calculated to be approximately 0.20 ml/min/kg and 20 h, respectively. In patients with GH receptor deficiency, there was a much more rapid turnover of rhIGF-I. The clearance and half-life were calculated to be 0.60 mg/min/kg and 6 h, respectively. Ranke has suggested that this increased clearance and decreased half-life is likely the result of the low concentrations of IGFBP-3 in this condition [24].

The pharmacokinetics of rhIGF-I–rhIGFBP-3 were studied by Barr and colleagues in healthy adult volunteers [25]. In this study, IGF-I levels

maintained a plateau of approximately 8–36 h, with a calculated half-life of 27.6 h. In prepubertal children with GHRD, the calculated half-life was 13.4 h [26]. A Phase I study of rhIGF-I–rhIGFBP-3 in adolescents with GHRD was reported by Barr and colleagues [25]. In that study, dose-dependent increases in IGF-I levels were observed and the half-life was estimated to be 21 h. The differences in half-life in these various patient populations is probably explained by the relative concentrations of circulating ALS.

Beyond its potentially superior side-effect profile when compared with free rhIGF-I, administration of the rhIGF-I–rhIGFBP-3 complex to patients with GHRD may also function in a more physiological way *in vivo*. IGFBP-3 is the principal carrier for both IGF-I and -II in the circulation. Administration of IGF-I alone actually decreases serum concentration of IGF-II in patients with diabetes, presumably by displacing IGF-II from IGFBP-3. The consequence of IGF-II release in the circulation is not well established in humans. Nevertheless, co-administration of rhIGF-I–rhIGFBP-3 would not result in significant displacement of IGF-II or endogenous IGF-I from circulating IGFBPs. Treatment of patient with GHIS with IGF-I has been shown to raise basal levels of IGFBP3 and ALS [27], and long-term IGF treatment raises basal IGF-I levels [28]. Moreover, administration of rhIGF-I–rhIGFBP-3 adds a 'buffer' effect, in that this complex can form a trimer with the ALS, an 85-kD protein, which then extends the circulating half-life of the bound IGF-I. By increasing the circulating pool of IGF-I in the ternary complex, a greater systemic exposure would be facilitated, which may then provide a more physiological delivery of IGF-I to important target tissues.

Clinical efficacy

Phase II studies

The first clinical use of rhIGF-I was in the treatment of GHRD (also known as GHIS or Laron syndrome). GHRD is characterized by growth failure starting in infancy that does not respond to GH administration, and is associated with normal or elevated levels of GH and decreased levels of IGF-I and IGFBP-3 [5,29]. Most of these trials began in the late 1980s and involved once- [30,31] or twice-daily dosing [32] of IGF-I, with equivalent responses [33]. Rosenbloom has reviewed results of rhIGF-I therapy in patients with GHRD [6]. Doses of 80–240 µg/kg/day have resulted in increases in linear growth. From reports of trials from 1993–1997, the growth velocity increased from 3.6 cm/year (range: 2.9–4.7 cm/year) to a mean of 8.4 cm/year (range: 7.2 – 9.3 cm/year) during the first year of treatment [6,32,34]. Azcona [34] and Backeljauw [35] have reported on the longer-term treatment of GHRD in a European cohort of 17 patients [36] and a US cohort of 8 patients [35], respectively, and have demonstrated sustained catch-up growth with a change in mean height standard deviation (SD) from -6.2 to -4.2 and maintenance of the mean growth velocity at 6.3 cm/year. Some patients achieved adult heights at the third centile.

Another potential category of patient that has been considered for treatment with IGF-I is those with lack of IGF-I due to *IGF-I* gene deletion. In 1996, a boy aged 15 years was described who had a deletion of the *IGF-I* gene [8]. Findings included severe intrauterine growth retardation, deafness, dysmorphic features, short stature and developmental delay. Serum IGF-I was undetectable, but he had normal serum levels of IGFBP-3 and elevated serum levels of IGF-II, ALS and GH. He was treated with IGF-I from 16 years of age, which resulted in an increase in growth velocity from 3.8 to 7.3 cm/year. Treatment also suppressed GH to normal [22] and reduced the patient's insulin resistance [37].

A third group of patients that have been considered for IGF-I therapy to improve growth includes patients with idiopathic short stature (ISS). ISS is a heterogeneous population, generally describing children with growth failure who are not GH deficient and who do not have a clear etiology for their short stature. ISS was approved as an indication for therapy with rhGH by the FDA in 2003. There continues to be interest in treating this group of children with rhIGF-I, since many of the patients who fall into this category have low IGF-I levels. Savage and colleagues have suggested that the most difficult obstacle in treating patients with ISS with rhIGF-I is that we do not have diagnostic methods sufficiently reliable to identify those patients who would benefit from this therapy [32].

In order to determine whether partial GH insensitivity was responsible for growth failure in children who were not GH deficient, data were analyzed from a large postmarketing study

of children who were being treated with GH [9]. The patients enrolled in this substudy had levels of IGF-I and GHBP determined and had been evaluated for GH deficiency by response to provocative stimuli. The strategy was to identify patients who had normal-to-elevated responses, in terms of GH, but low levels of IGF-I and GHBP. It was determined that patients who had low levels of GHBP had lower levels of IGF-I, as well as higher mean 12-h levels of GH. A subset of these patients (14 patients) were further studied and in this group it was possible to demonstrate that four patients had mutations in the GH receptor (but not in 24 control subjects) [38]. One of these patients was a compound heterozygote with respect to the GH receptor; one of the mutations resulted in reduced affinity of the receptor for GH and the other affected function without altering ligand binding. The three other patients had a single mutation in one allele of the GH receptor gene. These data seem to suggest that some patients with ISS may have partial GH insensitivity due to heterozygous mutations in the GH receptor gene.

Phase III studies

Results of a multicenter study involving the treatment of severe primary IGF-I deficiency with mecasermin rinfabate have been presented [39,40]. Two doses were used (cohort 1: ≤1 mg/kg and cohort 2: ≤2 mg/kg), administered as a single daily injection. Mecasermin rinfabate 1 mg contains IGF-I 210 µg. In cohort 1, the growth velocity increased from 3.4 ± 1.9 cm/year pretreatment to 6.4 ± 1.6 cm/year after 1 year of treatment with rhIGF-I–rhIGFBP-3. Cohort 2 demonstrated an increase from 2.0 ± 1.5 to 8.3 ± 2.1 cm/year with 1 year of treatment with IGF-I–IGFBP-3. 1 year of therapy resulted in an increase in height standard deviation scores (SDS) of 0.5 ± 0.4 ($p < 0.002$) for cohort 1 and 0.7 ± 0.6 ($p < 0.01$) for cohort 2. Bone age advanced 1.4 years during the first year of treatment. During therapy, IGF-I levels increased into the low normal range. There was no difference in response between genetic and acquired forms of severe primary IGFD (GHIS). Once-daily dosing was associated with 95% compliance.

Safety & tolerability

Treatment of GHRD with rhIGF-I has resulted in a number of mild-to-moderate adverse events. Most commonly reported adverse events have included pain at the injection site and headaches. The European study reported that these events seem to occur during the first month of treatment and then improved [36]. Other adverse events reported following rhIGF-I therapy have included lipohypertrophy at the injection site, papilloedema related to increased intracranial hypertension [41,42] and facial nerve paralysis. With these events, symptoms resolved after interrupting treatment and restarting with a lower dose [36]. Adverse events with mecasermin rinfabate have included injection site reactions, such as erythema, lipohypertrophy and hair growth [40].

A second concern has been hypoglycemia. It occured in some of the patients receiving rhIGF-I [29], but only rarely resulted in seizures [35] or loss of consciousness. This problem was lessened by administering the rhIGF-I dose with meals, and hypoglycemia was usually a problem when there was an intercurrent illness resulting in loss of appetite. With mecasermin rinfabate, hypoglycemia has been reported, but it has been described as generally mild and asymptomatic [40].

Another effect of rhIGF-I therapy has been growth of lymphoid tissue, in particular splenic enlargement and adeno–tonsillar hypertrophy, which has also been reported with mecasermin rinfabate [40]. Renal size also increased, but renal function remained normal [35]. There were also changes in facial appearance reported with rhIGF-I, with coarsening of features and an increase in hair growth, which were most noticeable during puberty [35].

Headache (but not intracranial hypertension) has been reported with both rhIGF-I and mecasermin rinfabate. Antibodies to rhIGF-I–rhIGFBP-3 were not associated with adverse events or growth attenuation [40].

As noted above, when the rhIGF-I–rhIGFBP-3 complex was administered in various Phase II and Phase III studies for various conditions, the reported side-effect profiles were generally improved over the side-effect profiles seen with the use of rhIGF-I alone.

Conclusion

rhIGF-I provides treatment for GH-resistant syndromes and has been reported to be effective in increasing growth velocity in patients with GH receptor abnormalities and a partial *IGF-I* gene deletion. Other conditions in which rhIGF-I may have a clinical utility include burns, osteoporotic fractures and Type 1 and 2

diabetes mellitus. The half-life of rhIGF-I is shorter in patients with low IGFBP-3 and/or ALS levels (such as those with GHIS), requiring two injections per day for optimal growth response, but patients with normal IGFBP-3 levels may be able to receive daily injections. Of particular benefit, mecasermin rinfabate (rhIGF-I–rhIGFBP-3) can be administered on a once-daily schedule because of the presence of rhIGFBP-3 in an equimolar amount with rhIGF-I. Hypoglycemia is an adverse event associated with administration of free rhIGF-I, which is likely attenuated by the presence of either endogenous or exogenous IGFBP-3.

Expert commentary

Mecasermin rinfabate has a clear place in treatment of GH-resistant syndrome, and may be preferred over rhIGF-I alone in patients with severe GH-resistance syndromes who have low endogenous IGFBP-3. However, this is a very small market (probably representing fewer than 500 patients worldwide). It remains to be shown whether there is a place for this medication in the treatment of other growth disorders, such as ISS with low IGF-I levels; there may be some children who are partially resistant to GH. However, at least in the near future, GH will probably remain the treatment of choice, unless it can be shown that rhIGF-I-containing therapies have an advantage. It seems likely that greater use may be found in treating other disorders that would benefit from the anabolic effects of mecasermin rinfabate, such as burns and osteoporotic fractures. It may also be useful for glucose management in Type 1 and 2 diabetes mellitus and in conditions of severe insulin resistance. Also, more experience is needed with mecasermin rinfabate to determine whether it is as effective or superior to IGF-I alone.

Future perspective

It is likely that there will be other uses of mecasermin rinfabate in addition to treatment of severe primary IGF-I deficiency in 5 years time. Possible uses include burns and osteoporotic fractures. It is also likely that this medication may be useful for glucose management in both Type 1 and 2 diabetes mellitus.

Executive summary

- Severe primary insulin-like growth factor (IGF)-I deficiency and *IGF-I* gene deletions are rare disorders, probably limited to fewer than 500 individuals worldwide.
- Recombinant human (rh)IGF-I-containing therapies now provide a useful treatment for severe primary IGF-I deficiency and *IGF-I* gene deletions.
- Mecasermin rinfabate, an equimolar mixture of rhIGF-I and its primary binding protein (rhIGFBP-3), appears to extend the half-life of administered rhIGF-I, allowing once-daily dosing in patients who are deficient in IGFBP-3 (while administration of rhIGF-I alone requires twice-daily dosing). Although it has not yet been shown definitively, it is possible that mecasermin rinfabate may result in fewer adverse events than administration of rhIGF-I alone.
- Ultimately, mecasermin rinfabate may have uses other than just treatment of severe primary IGF-I deficiency, such as other growth disorders, burns, osteoporotic fractures and both Type 1 and 2 diabetes mellitus.

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