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Rapid communication

Effects of 17 months treatment using recombinant insulin-like growth factor-I in two children with growth hormone insensitivity (Laron) syndrome

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Summary

OBJECTIVE With the availability of recombinant insulin-like growth factor-I (recIGF-I), it was possible to study whether this peptide could promote growth without noticeable side-effects in patients with growth hormone insensitivity syndrome (Laron syndrome). We report data obtained before and during 17 months treatment using recIGF-I, 40 μg/kg s.c. twice a day, in two Lebanese siblings.

PATIENTS The boy and the girl showed very short stature (−6·8 and −6·1 SDS), high GH (79 and 147 IU/l), low plasma IGF-I (0·12 and 0·18 U/ml) and undetectable GH-binding protein. Height velocities were 4·3 and 3·8 cm/year before treatment which started at 8·4 and 6·8 years of age, respectively.

RESULTS After 1–8 weeks of therapy, biological evidence of IGF-I effect was obtained from reduction in serum GH and increase in procollagen-I. During the first 6 months of treatment, height velocity increased to 7·8 and 8·4 cm/year without any clinical evidence of side-effects. Between 6 and 12 months, growth response decreased to 6·6 and 6·3 cm/year. Between 12 and 17 months, growth rate returned to pretreatment values. Changes in bone mineral density paralleled growth response and bone maturation increased by 1·5 and 2·0 years during the first 12 months of treatment. Daily assessment of blood sugar showed asymptomatic low values (< 2·8 mM/l) in 11/730 and 22/730 measurements in the boy and the girl, respectively.

CONCLUSIONS Treatment of two patients with growth hormone insensitivity syndrome using 40 μg/kg of IGF-I twice a day resulted in increased linear bone growth and bone mineralization as well as increased bone maturation without remarkable adverse events. After 1 year of therapy, growth response could no longer be observed in these two patients.

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In patients with Laron type of growth hormone insensitivity syndrome (GHIS), severe growth retardation results from abnormal or deficient GH receptors (Laron *et al.*, 1966; Eshet *et al.*, 1984). GH-binding protein (GHBP) which is consistent with the extracellular domain of the GH receptor (Baumann *et al.*, 1986) was shown to be undetectable in the majority of patients with GHIS (Daughaday & Trivedi, 1987; Baumann *et al.*, 1987). These patients were characterized by low IGF-I and high GH concentrations in serum. In short-term studies of the effects of recombinant IGF-I (recIGF-I) administration to patients with GHIS, it was suggested that such treatment could be considered for growth promotion on a long-term basis (Laron *et al.*, 1988, 1991; Walker *et al.*, 1991). More recently, growth velocity was shown to increase by 1·5–2·5 times during 9–10 months therapy in two patients studied by Laron *et al.* (1992) and one patient studied by Walker *et al.* (1992). Here, we report on the effects of treatment for 17 months in two siblings with GHIS.

Patients and methods

Patients

An 8.4-year old boy and his 6.8-year old sister from Lebanon were studied. Their parents were first cousins. Both children were born full term after normal pregnancy and delivery with birth weight of 3·5 kg. There was no history of hypoglycaemia. The boy had micropenis and bilateral cryptorchidism treated surgically at 4 years of age. The patients arrived in Belgium when they were 7·2 and 5·6 years old, respectively. The two patients were referred for short stature. They had clinical features consistent with severe GH deficiency or insensitivity. In the boy and the girl, GH concentrations were high (79 and 147 IU/l) with low plasma IGF-I concentrations (0·12 and 0·18 U/ml, respectively).

Diagnosis was confirmed by undetectable GHBP (courtesy of Dr M. C. Postel-Vinay, Paris, France). Both patients were included in a multicentre trial set up by Kabi Pharmacia, Stockholm, Sweden. At onset of IGF-I therapy, the

patients were respectively 8·4 and 6·8 years. Height was 88·9 (−6·8 SDS) and 85·7 cm (−6·1 SD), weight 12·8 (96% of ideal body weight, IBW) and 11·6 kg (94% of IBW) and bone age 5.1 and 3.4 years. Written informed consent of the parents was obtained. This study was approved by the local hospital ethical committee, University of Brussels.

Methods

IGF-I therapy was initiated during a 1-week period of in-patient monitoring of clinical and biochemical parameters. The patients were then seen regularly at 1-week to 3-month intervals. Height was measured using a Harpenden stadiometer. Subscapular skinfold was estimated by a single trained observer. Using height and weight, the body mass index (BMI) was calculated (Rolland-Cachera *et al.*, 1982). Morning blood samples were obtained in fasting conditions for measurements of serum glucose, triglycerides, total cholesterol, urea, creatinine, potassium and insulin. Serum concentrations of the C-terminal propeptide of GH and IGF-I (acid–ethanol extracts of serum) were measured in our laboratory. Serum concentrations of procollagen-I were determined using a highly specific radioimmunoassay (Farmos Diagnostica, Turku, Finland). Bone age radiographs were obtained every 6 months and bone maturation was estimated according to Tanner *et al.* (1983). Before therapy and after 3, 6 and 12 months of recIGF-I administration, bone mineral density (BMD) of lumbar spine was studied by dual photon absorptiometry using a Hologic QDR 1000 densitometer (Hologic Inc., Waltham, USA). Results were expressed in g/cm^2 and calculated as a percentage relative to pretreatment data. In our hands, the in-vitro coefficient of variation was 0·4% while others reported an in-vivo reproducibility of 1% in adults (Pacifici *et al.*, 1988). The presence of anti-IGF-I antibodies was investigated using a two-step radioimmunoprecipitation assay (Kabi Pharmacia, Stockholm, Sweden).

Therapy using recIGF-I (Kabi Pharmacia) was given as two daily subcutaneous injections initiated during a 1-week hospital stay. Capillary blood glucose levels were measured twice a day before injections of IGF-I which were performed before breakfast and supper. During the first week, glucose levels were measured every hour during a 5-hour period after each s.c. recIGF-I injection. In addition, after 9 months of therapy, glucose as well as electrolytes were measured 2, 4 and 8 hours after recIGF-I injection. The family was educated about signs of low blood sugar and correction with oral sugar or glucagon injection (Novo-Nordisk, Copenhagen, Denmark). In addition, snacks were given between the main meals.

Results

In the boy and the girl, height velocity was 4·3 and 3·8 cm/year before therapy and it showed a 1·8–2·2-fold increase during the first 6 months of recIGF-I therapy (Table 1). Between 6 and 12 months of therapy, height velocity was less rapid while no difference *vs* pretreatment height velocity was seen between 12 and 17 months. As shown in Fig. 1, no

Table 1 Height velocity in two patients with GH insensitivity syndrome before and during treatment using recIGF-I (80 μg/kg/day)

		Time during therapy (months)		
	Pretreatment	0–6	6–12	12–17
Boy (cm/year)	4·3	7·8	6·6	3·6
Girl (cm/year)	3·8	8·4	6·3	4·3

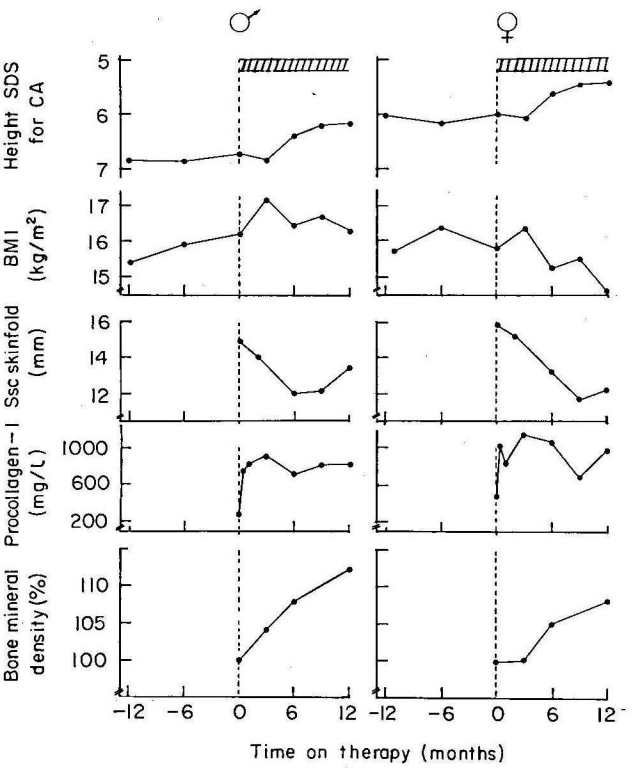

Fig. 1 Height SDS for chronological age, body mass index, subscapular skinfold, serum concentrations of procollagen-I and change in bone mineral density (percentage of initial value) in relation to time before and during 1 year of recIGF-I therapy (hatched bar 40 μg/kg s.c., b.i.d.) in two patients with GH insensitivity syndrome.

Table 2 Biochemical features in two patients with GH insensitivity syndrome treated using recIGF-I 40 μg/kg bid for a year

	Time during therapy (months)													
	Patient 1 (M)							Patient 2 (F)						
	−12	0	1	3	6	9	12	−12	0	1	3	6	9	12
Fasting glucose (3·8–6·1 mM/l)	3·7	3·5	5·4	4·0	4·6	3·9	4·7	3·9	3·8	4·7	5·1	3·8	3·4	3·9
Insulin (0–144 pM/l)	38	18	31	20	19	17	17	13	21	17	19	17	20	12
Triglycerides (0·17–1·78 mM/l)		0·69	0·77	0·68	0·77	1·34	0·81		0·91	0·77	0·91	0·77	1·23	0·91
Total cholesterol (< 5·17 mM/l)	5·95	5·48	5·56	5·25	5·22	5·61	5·09	4·94	5·20	5·12	4·65	4·97	5·17	4·32
Urea (1·8–8·9 mM/l)		13·2	10·0	11·1	7·5	6·8	10·7		10·7	8·9	10·7	10·7	7·9	9·6
Creatinine (27–80 μM/l)		53	35	42	35	53	42		53	42	42	35	42	27
K^+ (3·5–4·8 mM/l)	4·1	4·1	4·3	4·6	4·1	4·1	4·4		4·0	4·5	4·7	4·5	4·8	4·6

Normal range is given between parentheses.

significant growth response was observed after the initial 3 months of therapy though this could have resulted from measurement error. As a consequence of the changes in growth rate, height SDS for chronological age increased prominently during the first 6 months of therapy (Fig. 1). During therapy, some reduction in BMI and subscapular skinfold was seen, particularly between month 3 and 9 of therapy (Fig. 1).

Evidence of an early IGF-I effect was obtained through increase in serum concentrations of procollagen-I in both patients (Fig. 1). Pretreatment serum concentrations of GH were 79 and 147 IU/l in the boy and the girl, respectively and they decreased to a mean of 32 and 80 IU/l during the first 5 days of therapy. Subsequently, these biological parameters remained at a plateau level. In the boy and the girl, velocity in bone maturation was 0.3 and 0.7 years/year of chronological age before therapy and increased to 1.5 and 2.0 during therapy, respectively. Pretreatment bone mineral density (BMD) was low in the boy and the girl (0·409 and 0·412 g/cm^2, respectively). After 3, 6 and 12 months of IGF-I therapy, BMD increased respectively by 4·2, 8·1 and 12·5% in the boy and 0·2, 5·1 and 8·3% in the girl (Fig. 1).

As shown in Table 2, no significant changes in fasting serum concentrations of glucose, insulin, triglycerides, cholesterol, urea, creatinine or potassium were observed during therapy in either patient. During the first week of therapy as well as after 9 months, no hypoglycaemia was found during the 4-hour period following recIGF-I injection, except one single value at 2·5 mM 3 h after recIGF-I injection in the girl. Daily records of preinjection blood sugar showed values less than 2·8 mM/l in 11 out of 730 measurements in the boy and 22 out of 730 measurements in the girl. These episodes were asymptomatic and appropriately corrected with oral sugar supplementation. After correction of low blood sugar or at evening control in non-fasting conditions, some high values (> 10 mM/l, max 16 mM/l) were noted on two and eight occasions, respectively. Injections were reported to be tolerable and without any local sign of reaction. Compliance with treatment and blood glucose monitoring was excellent. Up to 9 months of therapy, no antibodies against IGF-I could be detected in the serum of either patient.

Discussion

In this paper, we provide further evidence that long-term administration of recIGF-I to patients with GHIS results in significant growth-promoting effects without major side-effects. This indicates that recIGF-I can stimulate growth through an endocrine mechanism and that this peptide is of potential therapeutic interest to increase growth rate in patients with insensitivity to GH, as recently proposed by others (Laron *et al.*, 1992; Walker *et al.*, 1992; Wilton, 1992).

Compared to the other studies using daily dosages of 150–240 μg/kg of recIGF-I (Laron *et al.*, 1992; Walker *et al.*, 1992), we used a lower dose of 80 μg/kg/day. Our data provide evidence of maximal growth and bone response to recIGF-I during the initial 6 months of therapy, this increased growth rate being seen prominently between months 3 and 6 of therapy. However, we obtained biological evidence of early bone effects of recIGF-I and other authors reported increase in height velocity from the beginning of recIGF-I therapy (Laron *et al.*, 1992; Walker *et al.*, 1992; Wilton, 1992). Therefore, it is possible that lack of measurement accuracy accounted for an apparent latency before increase in growth rate. More importantly, a rapid waning

effect seemed to occur after 6 months of IGF-I therapy. This reduction in growth response cannot be explained by compliance failure or immunization against recIGF-I. A growth response sustained for 9 months has been reported by Walker *et al.* (1992) though this period is too short to draw conclusions about a waning effect. Based on the preliminary data in single patients, it seems likely that a dosage of more than 80 μg/kg/day would be required to maintain significant growth response after 12 months of therapy.

Our study provides for the first time information on BMD and bone age velocity during treatment using recIGF-I. This therapy resulted in a significant increase in BMD and bone maturation showed a three to five-fold acceleration compared to pretreatment velocity. This raised the question whether increased sex steroids secondary to a direct gonadal effect of recIGF-I could account for such an increase in bone maturation (Adashi *et al.*, 1985; Chatelain *et al.*, 1991). However, such an explanation is unlikely since both patients remained prepubertal throughout the study. The changes in bone maturation will be important to take into consideration for IGF-I effects on ultimate height though this issue will possibly be addressed only with data from a long-term study of a large cohort of patients.

In our two patients treated using recIGF-I, the insulin-like effects were minimal as indicated by absence of symptomatic hypoglycaemia. In addition, during the first week of therapy as well as after 9 months, assay of blood sugar following recIGF-I injection showed only one asymptomatic low value. We cannot exclude asymptomatic hypoglycaemia since such assays were not performed on a daily basis. In contrast, fasting blood sugar was monitored daily. Few symptomless low blood sugar levels were observed. This could result from the GH-deficient-like status of our patients more likely than from an insulin-like effect of therapy. Unfortunately, we did not assess fasting blood glucose repeatedly before therapy. Other metabolic effects such as hyperglycaemia or hypokalaemia were minimal or absent during therapy. In addition, our patients did not complain about any symptoms. Appetite was unchanged. IGF-I could mediate the increased nitrogen retention and the reduced plasma urea nitrogen observed in GH-treated hypopituitary patients (Dahms *et al.*, 1989). Such a concept would be supported by the data of Walker *et al.* (1992) who found that, during recIGF-I therapy, serum urea nitrogen showed a reduction persisting after 71 days. We did not find any significant change in serum concentrations of urea nitrogen and creatinine, maybe because we used a lower dosage than Walker *et al.* (1992). Our data indicate that our treatment regimen was safe, though there are some questions about efficacy of the dosage used since the growth promoting effect could not be maintained in our study conditions.

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References

Adashi, E.Y., Resnick, C.E., D'Ercole, A.J., Svoboda, M.E. & Van Wyk, J.J. (1985) Insulin-like growth factors as intraovarian regulators of granulosa cell growth and function. *Endocrine Reviews*, **6**, 400–420.

Baumann, G., Shaw, M.A. & Winter, R.J. (1987) Absence of the plasma growth hormone-binding protein in Laron-type dwarfism. *Journal of Clinical Endocrinology and Metabolism*, **65**, 814–816.

Baumann, G., Stolar, M.W., Amburn, K., Barsano, C.P. & Devries, B.C. (1986) A specific growth hormone-binding protein in human plasma: initial characterization. *Journal of Clinical Endocrinology and Metabolism*, **62**, 134–141.

Chatelain, P.G., Sanchez, P. & Saez, J.M. (1991) Growth hormone and insulin-like growth factor I treatment increase testicular luteinizing hormone receptors and steroidogenic responsiveness of growth hormone deficient dwarf mice. *Endocrinology*, **128**, 1857–1862.

Dahms, W.T., Owens, R.P., Kalhan, S.C., Kerr, D.S. & Danish, R.K. (1989) Urea synthesis, nitrogen balance, and glucose turnover in growth-hormone-deficient children before and after growth hormone administration. *Metabolism*, **38**, 197–203.

Daughaday, W.H. & Trivedi, B. (1987) Absence of serum growth hormone binding protein in patients with growth hormone receptor deficiency (Laron dwarfism). *Proceedings of the National Academy of Sciences, USA*, **20**, 8–11.

Eshet, R., Laron, Z., Pertzelan, A., Arnon, R. & Dintzmann, M. (1984) Defect of human growth hormone receptors in the liver of two patients with Laron-type dwarfism. *Israel Journal of Medical Science*, **20**, 8–11.

Laron, Z., Anin, S., Klipper-Aurbach, Y. & Klinger, B. (1992) Effects of insulin-like growth factor on linear growth, head circumference, and body fat in patients with Laron-type dwarfism. *Lancet*, **339**, 1258–1261.

Laron, Z., Klinger, B., Erster, B. & Anin, S. (1988) Effect of acute administration of insulin-like growth factor I in patients with Laron-type dwarfism. *Lancet*, **ii**, 1170–1173.

Laron, Z., Klinger, B., Jensen, L.T. & Erster, B. (1991) Biochemical and hormonal changes induced by one week of administration of rIGF-I to patients with Laron type dwarfism. *Clinical Endocrinology*, **35**, 145–150.

Laron, Z., Pertzelan, A. & Mannheimer, S. (1966) Genetic pituitary dwarfism with high serum concentration of growth hormone. A new inborn error of metabolism? *Israel Journal of Medical Science*, **2**, 152–155.

Pacifici, R., Rupich, R., Vered, I., Fischer, K.C., Griffin, M., Susman, N. & Avioli, L.V. (1988) Dual energy radiography: a preliminary comparative study. *Calcified Tissue International*, **43**, 189–191.

Rolland-Cachera, M.F., Sempé, M., Guilloud-Bataille, M., Patois, E., Pequignot-Guggenbuhl, F. & Fautrad, V. (1982) Adiposity

indices in children. *American Journal of Clinical Nutrition*, **36**, 178–184.

Tanner, J.M., Whitehouse, R.H. & Cameron, N. *et al.* (1983) *Assessment of Skeletal Maturity and Prediction of Adult Height (TW2 Method)*. Second edition. Academic Press, New York.

Walker, J.L., Ginalska-Malinowska, M., Romer, T.E., Pucilowska, J.B. & Underwood, L.E. (1991) Effects of the infusion of insulin-like growth factor I in a child with growth hormone insensitivity syndrome (Laron dwarfism). *New England Journal of Medicine*, **324**, 1483–1488.

Walker, J.L., Van Wyk, J.J. & Underwood, L.E. (1992) Stimulation of statural growth by recombinant insulin-like growth factor I in a child with growth hormone insensitivity syndrome (Laron type). *Journal of Pediatrics*, **121**, 641–646.

Wilton, P. (1992) Treatment with recombinant human insulin-like growth factor I of children with growth hormone receptor deficiency (Laron syndrome). *Acta Paediatrica*, **383 (Suppl.)**, 137–141.