16

CHANGES IN BODY AND BONE COMPOSITION IN ADOLESCENT GROWTH HORMONE RECEPTOR DEFICIENT (GHRD) PATIENTS RECEIVING rhIGF-I AND A GnRH ANALOG.

J. Guevara-Aguirre(1), O. Vasconez(1), V. Martinez(1), A.L. Martinez(1), Z. Moreno(1), A.L. Rosenbloom(2), L. Bachrach(3), R.G. Rosenfeld(3).
IEMIR Quito-Ecuador(1), University of Florida, USA(2), Stanford University, USA(3).

We observed the body and bone composition changes in two adolescent GHRD patients receiving 120 ug/kg of rhIGF-I twice daily sc. A GnRH analog was administered im once monthly. LHRH testing demonstrated a blunted response during therapy. All safety parameters remain within normal ranges. The main characteristics of the individuals at baseline and at a six months evaluation are provided: SUBJECT #1: Age 17 8/12vs18 2/12 y; Height 115.5vs119.6 cm; Weight 28.6vs30.8 kg; BMI 30.0vs21.5; Bone age 13vs13 y; Body mass 28,604vs30,813 g; Lean mass 14,653vs16,891 g; Fat mass 13,951vs13,922 g; Fat percentage 48.8vs45.2 %; L/F ratio 1.05vs1.21; Body Calcium 326vs327; Total BMD 0.72vs0.83; Spine BMD 0.69vs0.70; Femur BMD 0.58vs0.63.
SUBJECT #2: Age 18vs18 6/12 y; Height 114.3vs118.4 cm; Weight 22vs21.7 kg; BMI 16.8vs15.47; Bone age 3.6vs13.6 y; Body mass 22,009vs21,674 g; Lean mass 13,146vs14,830; Fat mass 8,863vs6,844; Fat percentage 40.3vs31.6 %; L/F ratio 1.48vs2.16 g; Body Calcium 224vs240 g; Total BMD 0.7vs0.7 g/cm2; Spine BMD 0.65vs0.55 g/cm2; Femur BMD 0.59vs0.67 g/cm2.
Two adolescent patients receiving concomitant therapy with rhIGF-I and a GnRH analog for six months, showed an increase in height without an advancement in bone age. Body compositions changes included a decrease in body mass index, increments in lean mass, decreases in fat mass with associated height L/F ratio. Despite a diminishment in spine BMD in patient #2, bone mineral accretion was observed, with increases in total body mineral an calcium content, as well as in total and regional bone mineral density.

17

THERAPEUTIC RESPONSE TO RECOMBINANT IGF-1 IN THIRTY TWO PATIENTS WITH GROWTH HORMONE INSENSITIVITY

M.O. Savage[1], P. Wilton[2], M.B. Ranke[3], P.G. Chatelain[4], W.F. Blum[3], A.M. Cotterill[1], M.A. Preece[5], R.G. Rosenfeld[6]. St. Bartholomew's Hospital, London, UK[1], Kabi Pharmacia, Stockholm, Sweden[2], Children' Hospital, Tübingen, Germany[3], Hopital Debrousse, Lyon, France[4], Institute of Child Health, London, UK[5], Stanford University, California, USA[6].

30 patients with GH insensitivity syndrome (GHIS) (Laron syndrome) and 2 patients with GH gene deletion were included in a multicentre trial of recombinant human IGF-1 (rhIGF-1). The GHIS patients, from 9 European countries and Australia, were 15 of each sex, aged 3.7 - 22.9 y and 5 were pubertal. Clinical and endocrine features of GHIS were (median, range): Height SDS -6.7 (-9.1 to -3.2), basal GH 17 mU/L (2.4 - 208), IGF-1 21 μg/L (<20 - 69) and no response of IGF-1 to four days of GH (Genotropin^{R} 0.1IU/Kg/day). At baseline IGF-2 was 168 μg/L (43 - 295) and 19 had no measurable GH binding protein in serum. The GH gene deletion patients were a girl aged 14.2 y and a boy aged 16.7 y. 13 patients were initially started on rhIGF-1 40 μg/KG BWt s.c. bd, 7 increasing to 120 μg/Kg BWt bd at 3-6 months because of poor response. 17 GHIS and 2 GH gene deletion patients started on 120 μg/Kg BWt bd.

	Height Velocity							
Dose	Pre		6m		9m		12m	
(μg/Kg s.c. bd)	n=	cm/y	n=	cm/y	n=	cm/y	n=	cm/y
40	6	4.1	6	8.2	5	7.8	2	7.1,7.3
40-120	7	4.1	7	5.0	5	7.1	2	2.6,6.8
120	17	4.7	17	10.2	9	11.0	-	-
GH gene del.	2	1.4	2	8.4	1	10.0	1	9.4

Interestingly, despite an anabolic effect of rhIGF-1, serum levels of IGFBP-3, the principal carrier protein of IGF-1, did not change during treatment; basal was 0.69 mg/L (0.13 - 1.59), after 6 months therapy 0.46 mg/L (0.22 - 1.11). Hypoglycaemia (B.S. <3.0 mmol/L), with or without symptoms, occurred in 17 patients, 2 having consulsions. 12 patients reported mild or moderate headache, 1 severe with vomiting and bilateral papilloedema which resolved after discontinuation of rhIGF-1. 2 patients reported pain consistent with renal colic. 1 patient developed an unilateral Bell's palsy which resolved within 14 days.

CONCLUSIONS: rhIGF-1 in a dose of 40 - 120 μg/Kg BWt bd increased linear growth in children with GHIS and GH gene deletion. Serum IGFBP-3 did not change. This may contribute to hypoglycaemia, presumably related to high levels of free IGF-1. A growth promoting effect of this new therapeutic agent has been clearly demonstrated.

18

Z. Laron, B. Klinger
Children's Medical Center of Israel, Beilinson Campus, Petah Tikva Sackler Faculty of Medicine, Tel Aviv University, Israel

ONE YEAR TREATMENT WITH IGF-I OF CHILDREN WITH LARON SYNDROME (LS)

Having found that recombinant IGF-I acts in children with LS after acute (Lancet II: 1170, 1988), short term (Clin Endocr 36: 301, 1992) and long administration (Lancet 339: 1258, 1992), we continued treatment on a long-term basis. Forthwith the results of one year treatment of 8 prepubertal children (5 M, 3 F) with IGF-I (FK-780 Lot 115707K, Fujisawa Pharm. Co. Osaka, Japan, 120-150 ug/day s.c.). The mean (±SD) results for the whole group were:

Before Treatment					After Treatment				
C A	B A	Ht.	Gr.Vel.	S.S.	C A	B A	Ht.	Gr.Vel.	S.S.
yrs		SDS	cm/yr	mm	yrs		SDS	cm/yr	mm
8.2	5.8	-5.6	4.6	16.8	9.2	6.7	-5.1	8.4	13.1
(4.8)	(4.2)	(1.6)	(1.3)	(9.0)	(4.8)	(4.2)	(1.7)	(0.9)	(6.8)

It is evident that the growth velocity almost doubled (+80.2%), the mean height SDS improved by 0.6±0.5 in the presence of a normal bone age advencement. Body fat as measured by subscapular skinfold thickness (S.S.) decreased by a mean of 22% while mean body weight increased by 19.6%. The drug was well tolerated and keeping regular meals, no hypoglycemia were registered. The growth affected the extremities, the trunk and the headcircumference. The rise of serum procollagen I and III, Alk P-tase are similar to those found during hGH treatment of GH deficiency. Thus IGF-I mimics the effects of GH, proving that it is its true effector hormone.

Neuroendocrinology of Reproduction

19

REGULATION OF GnRH RELEASE FROM GnRH NEURONAL CELL LINES.

R.I.WEINER, Reproductive Endocrinology Center, University of California, San Francisco, Ca. 94143-0556, USA.

We previously developed the highly differentiated GT1 GnRH cell lines by genetically targeted tumorigenesis in transgenic mice. These cells express the GnRH gene and process the precursor peptide to GnRH. Cultures of GT1 cells form an interconnecting aborization of neuritic processes. GnRH release from these cultures is pulsatile with a pulse frequency identical to that seen in castrated mice. This finding demonstrates that the ability to generate and synchronize GnRH pulses is an intrinsic property of the cells. Numerous transmitters directly regulate GnRH release via receptors expressed on GT1 cells. Stimulatory regulators include norepinephrine, dopamine, and endothelin while vasopressin and prolactin suppress GnRH release. These findings support the concept that the regulation of GnRH release is highly pleiotropic. This work is supported by NIH Grant HD 08924.

20

KALLMANN SYNDROME: A DEFECT IN NEURAL TARGET RECOGNITION.

A. Ballabio[1], E. Rugarli[1], B. Lutz[2], S. Kuratani[2], S. Wawersik[2], G. Borsani[1], and G. Eichele[2]. [1]Institute for Molecular Genetics and [2]Department of Biochemistry, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.

Kallmann syndrome is a human genetic disorder characterized by a defect in olfactory system development due to an abnormality in the migration of olfactory axons and of gonadotropin releasing hormone (Gn-RH) producing neurons. The predicted protein product of the recently isolated gene for X-linked Kallmann syndrome shares motifs with molecules involved in neural development. We have isolated the chicken Kallmann syndrome gene which shows an overall 77% amino acid identity with the human homologue. The degree of identity increases within the putative functional domains, strongly supporting their functional relevance. Expression studies have been performed by Northern analysis, RT-PCR, RNase protection and in situ hybridization in chicken embryos at different developmental stages. In the developing and adult chicken, high levels of expression of this gene were found in the olfactory bulb and in the cerebellar cortex, both areas affected in patients with Kallmann syndrome. In the olfactory bulb, the gene is expressed by the mitral cells, the target of olfactory axons; in the cerebellum, expression was found in the Purkinje cells. The site and the timing of expression of the Kallmann syndrome gene within the olfactory system suggest that its protein product is a signal molecule required for proper neuronal targeting throughout life.