Recombinant human growth hormone

The identification, purification and later synthesis of growth hormone is associated with Choh Hao Li. Genentech pioneered the first use of recombinant human growth hormone for human therapy in 1981.

Prior to its production by recombinant DNA technology, growth hormone used to treat deficiencies was extracted from the pituitary glands of cadavers. Attempts to create a wholly synthetic HGH failed. Limited supplies of HGH resulted in the restriction of HGH therapy to the treatment of idiopathic short stature.

Very limited clinical studies of growth hormone derived from an Old World monkey, the rhesus macaque, were conducted by John C. Beck and colleagues in Montreal, in the late 1950s.

The study published in 1957, which was conducted on “a 13-year-old male with well-documented hypopituitarism secondary to a craniophyaryngioma,” found that: “Human and monkey growth hormone resulted in a significant enhancement of nitrogen storage … (and) there was a retention of potassium, phosphorus, calcium, and sodium. … There was a gain in body weight during both periods. … There was a significant increase in urinary excretion of aldosterone during both periods of administration of growth hormone. This was most marked with the human growth hormone. … Impairment of the glucose tolerance curve was evident after 10 days of administration of the human growth hormone. No change in glucose tolerance was demonstrable on the fifth day of administration of monkey growth hormone.”

The other study, published in 1958, was conducted on six people: the same subject as the Science paper; an 18-year-old male with statural and sexual retardation and a skeletal age of between 13 and 14 years; a 15-year-old female with well-documented hypopituitarism secondary to a craniopharyngioma; a 53-year-old female with carcinoma of the breast and widespread skeletal metastases; a 68-year-old female with advanced postmenopausal osteoporosis; and a healthy 24-year-old medical student without any clinical or laboratory evidence of systemic disease.

In 1985, unusual cases of Creutzfeldt–Jakob disease were found in individuals that had received cadaver-derived HGH ten to fifteen years previously. Based on the assumption that infectious prions causing the disease were transferred along with the cadaver-derived HGH, cadaver-derived HGH was removed from the market.

In 1985, biosynthetic human growth hormone replaced pituitary-derived human growth hormone for therapeutic use in the U.S. and elsewhere.

As of 2005, recombinant growth hormones available in the United States (and their manufacturers) included Nutropin (Genentech), Humatrope (Lilly), Genotropin (Pfizer), Norditropin (Novo), and Saizen (Merck Serono). In 2006, the U.S. Food and Drug Administration (FDA) approved a version of rHGH called Omnitrope (Sandoz).

A sustained-release form of growth hormone, Nutropin Depot (Genentech and Alkermes) was approved by the FDA in 1999, allowing for fewer injections (every 2 or 4 weeks instead of daily); however, the product was discontinued by Genentech/Alkermes in 2004 for financial reasons (Nutropin Depot required significantly more resources to produce than the rest of the Nutropin line).

In patients with Growth Hormone Deficiency (GHD), low doses of recombinant human Growth Hormone (rhGH) have a similar or better long-term clinical effect than higher doses. Pharmacogenetic studies suggest that Growth Hormone receptor (GHR) polymorphism influences only some metabolic parameters. Nonetheless there is no clear scientific evidence proving the effects of lower rhGH dose regimens on metabolic parameters. The aim of a prospective study was to evaluate the effects of GHR polymorphism in adult GHD patients treated with low rhGH dose during short (6 and 12 months) and long-term (5 years) follow-up.

Sixty-nine GHD adult patients were studied, before and during treatment with rhGH, using a standardized low-dose protocol calculated on the basis of body weight (0.01-0.03 mg/kg/week) and monitored by IGF-I plasma assay, anthropometric and metabolic parameters. The GHR genotype (flfl, fld3, or d3d3) was determined from peripheral blood.

d3-GHR carriers showed a more effective short and long-term response to low rhGH dose in LDL reduction, body composition and blood pressure (homozygous patients only); d3-GHR homozygosity is related to a significant IGF-I increase during short-term follow-up. Regression analysis demonstrated that rhGH dose, age at diagnosis and GHR genotype are the major determinants of IGF-I increase at 6 and 12 months of replacement therapy.

the d3d3-GHR genotype may influence some metabolic effects during short and long-term follow-up of low rhGH dose and could be an independent determinant of the increase of IGF- I during short-term follow-up [1)].

GH production rates markedly increase during human puberty, mostly as an amplitude-modulated phenomenon. However, GH-deficient children have been dosed on a standard per kg BW basis similar to prepubertal children. This randomized study was designed to compare the efficacy and safety of standard recombinant human GH (rhGH) therapy (group I, 0.3 mg/kg x week) vs. high dose therapy (group II, 0.7 mg/kg x week) in GH-deficient adolescents previously treated with rhGH for at least 6 months. Ninety-seven children with documented evidence of GH deficiency (peak GH in response to stimuli, <10 ng/mL), with either organic or idiopathic pathology, were recruited. Both groups were matched for sex (group I, 42 males and 7 females; group II, 41 males and 7 females), age [group I, 14.0+/-1.6 (+/-SD) yr; group II, 13.7+/-1.6], standardized height (group I, -1.4+/-1.1; group II, -1.2+/-1.1), bone age (group I, 13.1+/-1.3 yr; group II, 13.1+/-1.3) etiology, maximum stimulated GH, previous growth rate, and midparental target height. All subjects were in puberty (Tanner stage 2-5) at study entry. Of the 97 subjects enrolled, 45 were treated for 3 yr or more; 48 completed the study. Of the subjects who discontinued the study, the most common reason was satisfaction with their height, although others discontinued for adverse events or personal reasons. The frequency of patients who discontinued was the same in both groups. The primary efficacy analysis was the difference between dose groups for near-adult height, defined as the height attained at a bone age of 16 yr or more in males and 14 yr or more in girls; all subjects who qualified were included in the analysis. This difference was statistically significant at 4.6 cm by analysis of covariance (ANCOVA; $P < 0.001$; $n = 75$). For subjects who received at least 4 yr of rhGH treatment, the difference between dose groups at that time point was 5.7 cm (by ANCOVA, $P = 0.024$; $n = 20$). The mean height SD score at near-adult height was -0.7+/-0.9 in the standard dose group and 0.0+/-1.2 in the high dose group. At 36 months the cumulative change in height (centimeters) was 21.5+/-5.3 cm (group I) vs. 25.1+/-4.9 (group II; $P < 0.001$, by ANCOVA); the change in Bayley-Pinneau predicted adult height

was 4.8+/-4.2 cm (group I) vs. 8.4+/-5.7 (group II; P = 0.032). Median plasma IGF-I concentrations at baseline were 427 microg/L (range, 204-649) in group I and 435 microg/L (range, 104-837) in group II; at 36 months they were 651 microg/L (range, 139-1079) in group I vs. 910 microg/L (range, 251-1843) in group II (P = NS). No difference in change in bone age was detected between groups at any interval. High dose rhGH was well tolerated, with a similar safety profile as standard dose treatment and no difference in hemoglobin A1c or glucose concentrations between groups. In summary, compared to conventional treatment, high dose rhGH therapy in adolescents 1) increased near-adult height and height SD scores significantly, 2) did not increase the rate of skeletal maturation, and 3) appears to be well tolerated and safe. In conclusion, high dose rhGH therapy may have a beneficial effect in adolescent GH-deficient patients, particularly those who are most growth retarded at the start of puberty [2)].

Children with TS who were treated with rhGH exhibit an increased underlying risk for selected AEs associated with rhGH and for type 1 diabetes, which is likely unrelated to rhGH. The aortic dissection/rupture incidence reflects the higher baseline risk for these events in TS, was consistent with current epidemiological data in smaller TS populations, and is likely unrelated to rhGH. It is not known whether the reported malignancies represent an inherently increased risk in TS patients. Twenty years of experience in 5220 patients indicates no new rhGH-related safety signals in the TS population. The NCGS and similar registries, although focused on the years during rhGH treatment, may also be a window into the natural history of TS in childhood [3)].

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