Growth Hormone & IGF Research 25 (2015) 96–102

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

A pilot study of growth hormone administration in boys with predicted adult short stature and near-ending growth ☆

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ARTICLE INFO

Article history:
Received 24 June 2014
Received in revised form 16 January 2015
Accepted 19 January 2015
Available online 26 January 2015

Keywords:
Growth hormone
Boys
End of puberty
Idiopathic short stature

ABSTRACT

Context: The growth-promoting effect of starting recombinant human growth hormone (rhGH) at the time of near-ending growth has not been studied in sexually mature boys who will have idiopathic short stature (ISS) as adults because it is believed that such an advanced stage of puberty would preclude favorable results.
Objectives: 1) To explore the effects of starting rhGH administration at time of near-ending growth in boys with ISS. 2) To search for predictors of response to rhGH.
Subjects: Fifteen boys aged 15.5 ± 1 years terminating puberty were growing at a rate <2 cm/6 months towards a predicted adult height (PAH) <−2.5 SDS.
Methods: Participants received 0.50 ± 0.06 mg/kg·wk of rhGH according to a target-to-treat protocol. When growth became less than 0.5 cm in 3 months or when height has reached 169 cm, rhGH was ceased. Testosterone, growth velocity (GV), height, serum IGF-1, bone age (BA) at hand–wrist and knee score were measured at onset; IGF-1 and height were monitored every 3 months. A formula for PAH was developed. Height increment (HI, adult height-starting height) and height gain (HG, adult height-PAH) were calculated.
Results: Following rhGH administration for 11.1 ± 4.8 months, GV-SDS increased from −2.5 ± 1.7 to 3.5 ± 4.3 ($P = 2 \times 10^{-4}$), HI = 8.5 ± 3.7 cm, HG = 6.8 ± 4.8 cm and adult height was −1.8 ± 0.9 SDS, compared to a PAH of −2.9 ± 0.6 SDS ($P = 4 \times 10^{-4}$). Knee score ($P = 2 \times 10^{-3}$), GV at rhGH onset ($P = 8 \times 10^{-3}$) and rhGH dose ($P = 8 \times 10^{-3}$) were identified as predictors of HI and HG, but BA was not.
Conclusions: Our study suggests that 1) a short period of rhGH administration can increase true adult height significantly in boys with ISS at time of near-ending growth; and 2) knee score rather than BA should be used to identify rhGH responders. These preliminary observations await confirmation by larger randomized trials.

1. Introduction

The most common condition presented at a growth clinic is idiopathic short stature (ISS) [9]. Although the clinical effectiveness of recombinant human growth hormone (rhGH) in ISS is well documented [3,5,13–15,22–24,27,37], the use of this treatment varies largely across countries and health systems. For example the treatment of ISS with rhGH is not approved by the European Medicine Agency, whereas this indication has been approved in the United States since 2003, followed by a consensus on the management of ISS published in 2008 [9]. The prerequisites for the use of rhGH in ISS set by the Food and Drug Administration (FDA) are that other diagnoses are excluded, that the presenting height is <−2.25 SDS for age and sex, and that stature in adult life is expected to be <−2.0 SDS. A Cochrane review concluded that a mean gain in adult height of 7 cm can be expected from rhGH treatment of ISS, with individual gain ranging from 0 to 20 cm, as estimated by comparison with untreated historical or randomized controls, or with the predicted adult height of the children [5,9].

Peak growth velocity (PGV) occurs at 14–15 years in most European boys [1] after which growth velocity (GV) decreases rapidly [1,36]. When growth velocity has faltered under 3.5 cm per 12 months, cessation of growth can be expected to occur within 2 years [29,36]. Complete cessation of growth thus occurs between 16 and 18 years of age in most boys [17,29]. A fraction of sexually mature boys seek a growth-promoting treatment when they realize that their rapidly decreasing growth velocity will not allow them to reach an adult height

Abbreviations: ATO, age at take-off; APGV, age at peak growth velocity; BA, bone age at hand–wrist; FDA, Food and Drug Administration; GV, growth velocity; HG, height gain; HI, height increment; HTO, height at take off; ISS, idiopathic short stature; KS, knee score; PAH, predicted adult height; PGV, peak growth velocity; QOL, quality-of-life; RCT, randomized control trial; rhGH, recombinant human growth hormone; SDS, standard deviation score.

☆ Disclosure statement: The present study received no research grant from any industry. PB and AR have had no personal consultancy fees with any of the pharmaceutical companies selling rhGH for the past 5 years. PB's Inserm laboratory received grants from Pfizer, NovoNordisk and Ipsen for growth related and Type 1 diabetes translational research. BO and GK have nothing to declare.

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http://dx.doi.org/10.1016/j.ghir.2015.01.002
1096-6374/

acceptable for them. A flattening of the growth curve often comes as a surprise to these adolescents. This was the case in the current series of 15 adolescents with ISS who had not previously received rhGH. The growth-promoting effect of starting rhGH has not been studied in sexually mature boys with ISS, since it is generally felt that an advanced stage of puberty would preclude favorable results [15,26,27].

We first considered a randomized trial versus untreated controls, but after a few months of enrollment, we were faced with the primary refusal of adolescents who sought treatment at other growth clinics rather than accepting to stay in the untreated arm of our trial. We then decided to perform a comparison with predicted adult height (PAH). In addition, we tried to identify predictive factors that could help pediatricians to foresee the response of such adolescents to rhGH administration.

2. Methods

2.1. Subjects

We included all the adolescent boys who were seeking treatment at our growth center between January 2004 and September 2009 with the following criteria: i) testis volume > 12 ml and testosterone levels > 4 ng/ml (young adult levels) [19]; ii) an informative track of height measurements during puberty allowing calculation of growth velocity precisely; iii) no prior rhGH treatment; iv) a slow growth velocity (<2 cm/6 months); and v) a PAH at or under −2.5 SDS. We chose this height because a quality-of-life (QOL) study identified −2.5 SDS as the threshold for observing a negative impact of short stature on male adults [7]. Mid-parental height was not used to predict adult height because it does not take into account the individual tempo of puberty. Instead we developed a personalized algorithm allowing an accurate prediction of height (see "Modeling of growth") [20]. GH deficiency (GHD) was excluded by a stimulation test with a GH peak >15 ng/ml. A peak GH concentration less than 10 ng/ml after any one or more of series of secretagogues and assayed by RIA (radioimmunoassay) has traditionally been used to support the diagnosis of GHD [38]; however, the equivalent level in monoclonal-based assays is considered to be 7 ng/ml [4]. We chose 15 ng/ml as an arbitrary cut-off to safeguard the study from including adolescents with GHD. In addition, none of the participants had a basal serum IGF-1 concentration <−1.2 SDS. Subtle forms of dyschondrosteosis or other chondrodysplasia were excluded by examination of radiographs of the forearm, pelvis and spine. Thyroid stimulating hormone (TSH) levels were normal. All adolescents were healthy and clinical examination was normal.

Parents and adolescents were informed about the results of the available long-term rhGH safety studies [34] through oral interviews and written material. They knew the recommendations of the national agencies and were left a full month before making the treatment decision. They gave their written informed consent to the study according to the French rules of bioethics.

2.2. Growth hormone titration protocol

The 15 boys fulfilling the inclusion criteria were started on 70 μg rhGH/kg·d (=0.49 mg/kg·wk). Titration of rhGH dose was adjusted every 3 months to growth velocity and maintenance of IGF-1 level between 0.5 and 1.5 SDS, as previously reported [32], a compromise between the two IGF-1 titrating regimens proposed by Cohen et al. [8,10,11]. If the growth velocity was <1.5 cm/3 months, the rhGH dose was increased by 20% while maintaining serum IGF-1 below +1 SD. Treatment was stopped when the growth velocity stood below 5 mm in 3 months or when the adolescent has reached a height >169 cm. Patients were seen between 17.5 and 18.5 years for adult height measurement.

2.3. Studied parameters

At baseline, the following were measured: height, weight, serum testosterone, serum IGF-1, bone age at hand–wrist (BA), knee score and growth velocity. At each visit (every three months while on rhGH treatment), the following were measured: height, weight, serum IGF-1, and growth velocity. Height was measured (PB and AR did two measurements at the beginning and end of each visit) using a stadiometer having a 0.11% precision (SD/mean). Growth velocities were converted to cm per year even when measured over shorter periods of time. Growth velocity SDS was based on growth curves for French children [21]. Testis volume was evaluated with a direct measurement of their major and minor axes and calculation of the corresponding ellipsoid volume ($4/3\ \pi \times a \times b \times c$, with a, b, c being the radii).

Bone age at hand–wrist [18] and the degree of closing of the femoral inferior and tibial superior growth plates used to calculate the "knee score" (KS) as defined in [25,30] were evaluated by the same three independent investigators, blind to the patient's identity, and the values were averaged. The KS includes five stages of epiphyseal union at the knee joint ranging from 0 (non union) to 5 (complete epiphyseal fusion).

Testosterone was measured using direct RIA with Orion reagents (CisBio International, Gif sur Yvette, France). Sensitivity was 0.01 ng/ml (0.05 nmol/l). Serum IGF-1 levels were measured at 7.00–11.00 h am, 12–16 h after the previous evening rhGH injection. Values recorded every 3 months were used for monitoring rhGH treatment and were averaged to calculate individual IGF-1 means during rhGH administration. Serum IGF-1 was measured by immune-radiometric assay after ethanol–acid extraction using DSL-5600 Active reagents (Diagnostic Systems Laboratories, DSL, Webster, TX). IGF-1 SDS calculations were provided by DSL as reported [9,10]. Intra- and inter series coefficients of variation were 1.5 and 3.7% at 260 ng/ml, and 2.5 and 3.9% at 760 ng/ml. The sensitivity was 4 ng/ml. Mean IGF-1 values during the period of treatment are a mean of all IGF-1 values measured at each 3-monthly visit. Delta-IGF-1 and delta-IGF-1 SDS were calculated by subtracting IGF-1 at onset from mean IGF-1 during the year of rhGH treatment.

The following studied parameters were used to predict rhGH treatment efficacy: KS, growth velocity at rhGH onset, rhGH dose, BA, age at rhGH onset, time elapsed since PGV, age at PGV, testosterone level at rhGH onset and delta IGF-1.

Theoretical safety was assessed by the proportion of IGF-1 measurements above +2 SDS at the end of the treatment period, as proposed by Cohen et al. [11].

2.4. Modeling of growth

During the period preceding PGV, the growth trajectory could be modeled in all adolescents from their "Carnet de Santé" (Health Notebook), a national pediatric booklet where height and weight are reported by pediatricians or general practitioners during the whole period of growth [31]. The pubertal growth spurt trajectory was defined by the height and age at the two inflection points that mark the onset of acceleration (take off) and onset of deceleration (peak growth velocity, PGV), (Fig. 1 and Table 1B).

Instead, we took advantage of the slow and decelerating growth velocity recorded in all participants to predict final height. We modeled the deceleration of growth velocity using the age (t) and height (h) of each subject accurately measured during the deceleration period. We considered that growth velocity after PGV slows uniformly and becomes 0 cm/year at an age t_{fin} being 2 years from PGV [35] (see Fig. 1). The initial slope b of the curve is approximated from the recorded values at PGV, (t_1, h_1), and rhGH onset, (t_2, h_2), as

$$b = (h_2 - h_1)/(t_2 - t_1).$$