Lucia Schena, Cristina Meazza, Sara Pagani, Valeria Paganelli, Elena Bozzola, Carmine Tinelli, Fabio Buzi and Mauro Bozzola*

Efficacy of long-term growth hormone therapy in short non-growth hormone-deficient children

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Abstract

Background: In recent years, several studies have been published showing different responses to growth hormone (GH) treatment in idiopathic short stature children. The aim of the present study was to investigate whether non-growth-hormone-deficient (non-GHD) short children could benefit from long-term GH treatment as GHD patients.

Methods: We enrolled 22 prepubertal children and 22 age- and sex-matched GHD patients, with comparable height, body mass index (BMI), bone age, and insulin-like growth factor 1 (IGF-I) circulating levels. The patients were treated with recombinant human GH (rhGH) and followed until they reach adult height.

Results: During GH treatment, the two groups grew in parallel, reaching the same final height-standard deviation score (SDS) and the same height gain. On the contrary, we found significantly lower IGF-I serum concentrations in non-GHD patients than in GHD ones, at the end of therapy ($p = 0.0055$).

Conclusions: In our study, the response to GH treatment in short non-GHD patients proved to be similar to that in GHD ones. However, a careful selection of short non-GHD children to be treated with GH would better justify the cost of long-term GH therapy.

***Corresponding author: Mauro Bozzola,** Professor, Dipartimento di Medicina Interna e Terapia Medica, Unità di Pediatria e Adolescentologia, Università degli Studi di Pavia, Fondazione IRCCS San Matteo, Piazzale C. Golgi 19, 27100 Pavia, Italy, Phone: +39 0382 501270, Fax: +39 0382 502876, E-mail: mauro.bozzola@unipv.it
Lucia Schena, Cristina Meazza, Sara Pagani and Valeria Paganelli: Department of Internal Medicine and Therapeutics, Unit of Pediatrics and Adolescentology, University of Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
Elena Bozzola: Department of Pediatrics, Pediatric and Infectious Diseases Unit, Bambino Gesù Children's Hospital, Rome, Italy
Carmine Tinelli: Clinical Epidemiology and Biometric Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
Fabio Buzi: Department of Pediatrics, "Carlo Poma" Hospital, Mantova, Italy

Keywords: adult height; growth hormone; growth hormone treatment; insulin-like growth factor-I; short stature.

Introduction

Idiopathic short stature (ISS) children belong to a heterogeneous group of subjects with impaired growth and blunted growth velocity, but normal growth hormone (GH) secretion [1]. By definition, an individual is classified as having ISS if his/her height is 2 standard deviations (SDs), or more, below the mean height for a given age, sex, and population group in the absence of systemic, endocrine, nutritional, or chromosomal abnormalities. Approximately 23 per 1000 individuals have this diagnosis [2]. This relatively common condition may include both constitutional delay of growth and puberty and familial short stature.

In 2003, the US Food and Drug Administration (FDA) approved the use of GH for the treatment of ISS in children whose height was more than 2.25 SD score (SDS) below the mean for age and sex without evidence of an underlying disease or GH deficiency (GHD). Furthermore, the FDA issued a statement that these children should have a growth rate unlikely to assure an adult height within the normal range (160 cm for men and 150 cm for women) [3].

In the last few years, several studies have been published showing the response to GH treatment in these subjects. Some of these studies demonstrated higher mean adult height in treated children [4–6], while other studies did not find an effect of GH treatment on adult height [7, 8]. However, such different results may be explained by the variable GH dosing and administration schedule.

We have previously shown that short children with normal GH secretion can benefit from short- and long-term GH treatment as GHD patients do [9, 10]. Furthermore, in these patients, the optimal GH regimen in terms of cost-effectiveness is still debated due to a lack of controlled trials with a follow-up through final height [6].

The aim of the present study was to investigate whether short children presenting auxological criteria suggestive of GHD but normal GH response (non-GHD)

could benefit from long-term GH treatment as in GHD patients.

Patients and methods

We enrolled 22 prepubertal children (12 males and 10 females), age 11.32±2.35 (mean±SD) years, with a height at diagnosis of 127.2±13.1 cm (−2.2±0.7 SDS) and a normal GH response to pharmacological stimuli (>10 ng/mL), but circulating IGF-I values below the normal limit for sex and age (< −2 SDS) [11]. GH stimulation tests were performed by administering pharmacological stimuli such as arginine or glucagon according to the guidelines for the diagnosis and treatment of GHD in childhood [12]. During the same period, we enrolled 22 prepubertal age- and sex-matched GHD patients (12 males and 10 females), age 11.2±2.7 years, with a height at diagnosis of 129.6±16.6 cm (−1.65±1.44 SDS) and GH response <10 ng/mL to at least two pharmacological stimuli.

Standing height for all subjects was measured using a Harpenden stadiometer. Anthropometrical data and pubertal development stage were recorded according to Tanner charts [13].

No other causes of short stature such as adrenal and thyroid dysfunction, malabsorption such as celiac and Crohn's diseases, kidney and hepatic diseases, or hypocondroplasia were found. In females, Turner syndrome was excluded by high-resolution karyotype.

According to the international recommendations for the use of GH in children [12], recombinant human GH (rhGH) therapy was administered in idiopathic GHD children at a weekly dose of 0.21–0.23 mg/kg subcutaneously, divided into six daily doses in the evening. In non-GHD subjects, GH treatment was administered according to local protocols [14] and at the same dosage used in GHD children. In fact, in 2001, Agenzia Italiana del Farmaco (AIFA) published a note, called 39 Note, allowing GH treatment also in short children with normal GH response to pharmacological stimuli (>10 ng/mL) but with circulating IGF-I values below the normal limit for sex and age (< −2 SDS). Therefore, for some years, we have been able to start GH treatment of these children as in the GHD ones.

Before the start of treatment, oral administration of glucose excluded any status of glucose intolerance. During treatment, thyroid and adrenal functions and glycated haemoglobin levels were monitored every 6 months.

Serum GH and IGF-I were measured with a fully automated immunochemistry analyzer (Immulite 2000, Siemens Healthineers Italia, Italy). All the enrolled patients reached final height and the mean duration of treatment was 48 months (20 GHD and 20 non-GHD patients showed 60 months of follow-up).

Statistical analysis

Quantitative variables were expressed as mean values and SD as they were normally distributed (the Shapiro-Wilk test). To analyze the differences of quantitative variables between the two groups, a t-test for independent data was used; linear regression models for repeated measures were used to analyze the patterns of growth between groups over time, during GH therapy. Qualitative variables were summarized as counts and percentages and differences were evaluated with a χ^2-test. All of the tests were double-tailed and the limit of statistical significance was set to the commonly used 5% ($p<0.05$). Data analysis was performed with the software STATA (version 14, Stata Corporation, College Station, TX, USA).

Results

Auxological parameters of GHD and non-GHD patients are shown in Table 1. We enrolled prepubertal patients of comparable ages in order to eliminate the bias due to different ages, as short non-GHD patients are often diagnosed later than GHD ones. At diagnosis, non-GHD short children seemed to be shorter than GHD patients, although the difference was not statistically significant. Some patients entered puberty during follow-up, but these were equally distributed in the two groups. We found that target height in short non-GHD patients was significantly lower than in GHD patients. Moreover, at diagnosis, IGF-I levels and

Table 1: Auxological parameters of enrolled patients at the time of diagnosis.

	Non-GHD	N	GHD	n	p-Value
Birth weight, g	3120.5±579.5	22	3251.82±413.6	22	0.391
Birth length, cm	48.03±4.8	15	50.04±2.04	16	0.135
Target height (SDS)	−1.14±1.01	20	−0.52±0.69	21	0.026
Chronological age, years	11.32±2.35	22	11.24±2.67	22	0.919
Bone age, years	8.69±0.65	16	10.01±0.47	9	0.158
GH peak (ng/mL) after 1st stimulus	11.78±6.22	22	5.1±2.84	22	<0.0001
GH peak (ng/mL) after 2nd stimulus	15.9±4.6	11	6.7±2.6	22	<0.0001
Height (SDS)	−2.19±0.74	21	−1.65±1.44	22	0.129
BMI (SDS)	−1.03±1.11	21	−1.13±0.99	22	0.771
IGF-I (SDS)	−2.02±0.91	11	−1.32±1.03	5	0.196
Age at puberty, years	12.92±1.24	22	12.06±1.97	20	0.097

Data are expressed as mean±standard deviation.

bone age were not significantly different between the two groups of patients (Table 1).

With regard to the pattern of linear growth during GH therapy, we observed that height in GHD patients was always about 0.5 SDS higher than in non-GHD ones ($p < 0.005$). The two groups of patients grew in parallel reaching similar height-SDS after 60 months of therapy (non-GHD: -0.82 ± 0.29 SDS, GHD: -0.67 ± 0.12 SDS; $p = 0.670$). In the subsequent follow-up, the growth trend of GHD patients seemed to be better than that of non-GHD ones (Figure 1), although the two groups did not show any significant difference in the values of final height (non-GHD: -1.50 ± 0.21 SDS, GHD: -1.39 ± 0.30 SDS; $p = 0.752$) and in the height gain at the end of therapy (non-GHD: 34.72 ± 2.96 cm, GHD: 37.54 ± 3.65 cm; $p = 0.555$). On the contrary, we found significantly lower IGF-I serum concentrations in non-GHD patients than in GHD ones (-0.69 ± 1.18 and 0.36 ± 1.11 SDS, respectively; $p = 0.0055$).

Discussion

In this study, we compared the growth pattern of non-GHD and GHD children during GH therapy until they reached final height.

In fact, a previous short-term study of ours and other studies have demonstrated acceleration of growth rate following administration of rhGH to short normal children [9, 15, 16].

In the present study, at diagnosis, the two groups of patients were of comparable ages, bone ages, heights, and IGF-I circulating levels. We only observed a lower target height in non-GHD children compared with idiopathic GHD children. This finding could be due to the higher incidence of familiar short stature in non-GHD subjects.

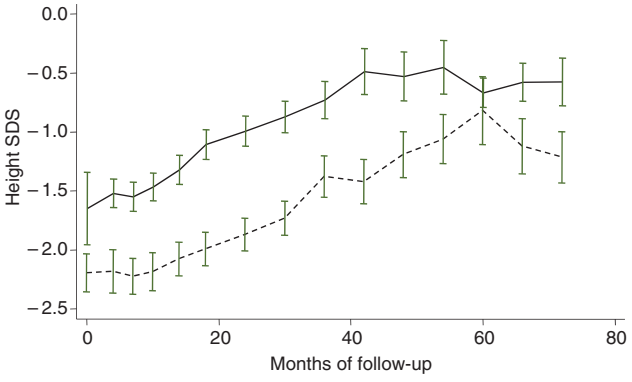

Figure 1: Height SDS trend during GH therapy in non-GHD (dotted line) and GHD patients (solid line).
Data are expressed as mean ± standard deviation.

We found a similar growth-promoting effect of the GH therapy in short non-GHD children in comparison with age-matched classical idiopathic GHD patients. In particular, in the first 60 months of treatment, both groups showed a significant and parallel improvement in height, even if GHD patients always remained about 0.5 SDS taller than short non-GHD ones. After this period of therapy, non-GHD subjects reached the same height observed in GHD patients, but subsequently showed a progressive decrease in growth velocity, while GHD patients maintained their growth rhythm for some years (though the number of patients whose therapy lasted more than 5 years was smaller). At the end of the therapy, the two groups reached a comparable final height and height gain, suggesting that the efficacy of the treatment in short non-GHD patients is similar to that of GHD subjects and that short non-GHD children would also benefit from GH treatment. In fact, GH-treated non-GHD patients show a final stature even greater than their target height.

Interestingly, at the end of the therapy, short non-GHD children showed lower IGF-I levels than GHD children, suggesting a form of GH resistance. In effect, a higher proportion of patients with ISS with decreased sensitivity to GH has been described [17]. This may be due, at least in part, to different heterozygous GH receptor mutations or defects in the modulation of the negative feedback regulation of the GH receptor (JAK-2/STAT-5 signalling pathway) [18, 19].

In the literature, many studies evaluating the effect of GH therapy on adult height in ISS have been published, albeit with contrasting results. Some studies concluded that GH treatment increases adult height. The one by Leschek et al. [5] demonstrated that GH treatment increases adult height in peripubertal children with marked ISS. Albertsson-Wikland et al. [6] showed that GH treatment significantly increased final height in ISS children in a dose-dependent manner. The mean height gain was 1.3 SDS (8 cm) vs. a mean gain of 0.2 SDS in the untreated controls, although there was a wide range of response from no gain to 3 SDS. In another small study, GH therapy effectively increased height SDS in short normal girls who were started on treatment in early to mid childhood, without any effect on pubertal progression [4]. Other studies show higher mean adult heights in treated participants who generally reach their target height and predicted height [15–23]. These authors conclude that therapy appears to be safe, notwithstanding that the more

efficacious doses of GH are higher than those used in GHD children [24]. However, they raise some concerns about the obtained results, stating that the high cost of the treatment should always be weighed against the results [16]. In fact, the small increment in final height (approximately 2.8 cm in boys and 2.5 cm in girls) does not justify the widespread use of rhGH for short normal children [25]. Finally, other authors found no effect of GH treatment on adult height [7, 8]. They showed that rhGH treatment in ISS children did not improve either height SDS during the prepubertal period or the average final height. The authors hypothesized that part of the heterogeneity of the response can be attributed to the variation in endogenous GH secretion and initial bone age delay in the children [7].

A joint consensus statement from the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society (now the Pediatric Endocrine Society), and the European Society for Paediatric Endocrinology concluded that the shorter the child, the more consideration should be given to treatment with GH, but they also stated that therapy would generally not be recommended for a short child who is unconcerned about his/her stature [2].

We consider it particularly important to carefully evaluate the characteristics of ISS children that should be treated with GH. In fact, we suggest that GH treatment is indicated only for short stature patients with peculiar auxological criteria, such as growth rate/year < -2 SDS, and low IGF-I levels (< -2 SDS).

In conclusion, in our study, the response to GH treatment in short non-GHD patients proved similar to that observed in age-matched GHD ones. On the other hand, GHD patients in this study maintained a better long-term growth gain compared to short non-GHD subjects. Furthermore, a careful selection of short non-GHD children to be treated with GH would better justify the cost of long-term GH therapy until attainment of final height.

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