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Original article

Effect of growth hormone treatment on children with idiopathic short stature (ISS), idiopathic growth hormone deficiency (IGHD), small for gestational age (SGA) and Turner syndrome (TS) in a tertiary care center

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Summary. *Objectives:* To assess the long-term effect of growth hormone (GH) therapy in a large cohort of short children with different etiologies. *Patients and Methods:* We evaluated retrospectively the anthropometric data of 252 short children [height SDS <-2: 154 children with growth hormone deficiency (GHD), 63 with idiopathic short stature (ISS), 26 with SGA, and 9 with Turner syndrome (TS)] who were treated, in our center, with GH between 1-2007 and 1-2018. Before and during recombinamt growth-hormone (recGH) treatment, auxological parameters including height (Ht), weight (Wt), Ht - Z score (HtSDS), body mass index (BMI) and BMISDS were recorded every 6 months; bone age (BA) was assessed every 12 months. *Results:* At the end of first year of rhGH therapy and after an average of 3 years treatment all groups of short children had significant increase in HtSDS, which was higher in GHD compared to other groups. Children with GHD, SGA, ISS and TS increased their HtSDS by an average of 2.2, 1.46, 0.6 and 0.99 SD, respectively at the end of follow up period (for all groups, p: <0.001). The bone age/chronological age (BA/CA) ratio did not differ significantly among ISS, GHD and SGA groups after GH therapy. The HtSDS gain was higher in children with GHD compared to other ISS, SGA and TS groups (p:< 0.01; p: 0.015 and p: 0.029, respectively). HtSDS improvement occurred during the first 3 years of rhGH therapy. The BMISDS increased significantly in children with GHD, after 3 years of rhGH therapy (p: < 0.001). After rhGH treatment, the BMISDS decreased significantly in children with ISS and SGA (p: < 0.01 and < 0.001, respectively) but did not change in children with TS (p: 0.199). *Conclusions:* Children with GHD, SGA, ISS and TS exhibited significant increases in HtSDS when treated with rhGH for 3 years. The HtSDS gain was higher in children with GHD compared to other groups. (www.actabiomedica.it)

Key words: linear growth, HtSDS, GH deficiency (GHD), idiopathic short stature (ISS), small for gestational age (SGA), Turner syndrome (TS), recombinant GH therapy (rhGH)

Introduction

Plentiful supply of recombinant growth hormone (rhGH), acquired via recombinant DNA technology, enabled the expansion of its use beyond replacement of deficient growth hormone (GHD) including short children with non-GH deficiency disorders. Short stature is defined as a height of less than -2 standard deviation (SDs) compared to the mean height at the corresponding age and sex.

Idiopathic short stature (ISS) is a short stature condition in children with a normal birth weight,

normal body proportions, normal GH response to stimulation tests, height SDS corresponds to mean parental SDS, and no identified cause for their short stature. However, ISS children represents a heterogeneous group of children with many non-specific causes of short stature. Children with familial short stature and constitutional delay of growth and puberty are included in the ISS category. In 2003, the United States Food and Drug Administration approved the use of rhGH for children with a height SD score (HtSDS) of less than -2.25 and a short predicted adult height (PAH) (1-5).

In addition, clinical data showed that rhGH is an effective therapy for short children who are born small for gestational age (SGA). Therefore, short children born SGA who fail in their catch-up growth by 2-4 years of age are candidates for rhGH therapy. It has been shown that, in SGA children, the response to rhGH therapy varies with GH status. Therefore, it has been recommended that GH status be assessed in patients born SGA to optimize rhGH treatment (6,7).

Several studies have shown that rhGH therapy increases adult stature in TS, and this therapy is approved by the U.S. Food and Drug Administration (FDA) and other regulatory agencies worldwide with variable results on final adult height (8,9).

Few previous clinical data have been compared the growth response to long-term rhGH therapy in short children with ISS, TS and SGA to those with isolated GHD. Here, we present and compare the effects of GH treatment in children with ISS, TS and SGA in comparison to those with GHD, treated in a tertiary care center (10).

Patients and methods

1. Patients

We retrospectively reviewed the medical records of 252 children with short stature (height SDS <-2) who were diagnosed and treated, between January 2007 till January 2018, in our tertiary care center with rhGH. Children with organic brain lesions, systemic diseases, or syndromes that result in growth disorders (apart from TS) were excluded.

Idiopathic short stature was diagnosed, in whom with no identifiable disorder, when the height of the child was more than 2 SD below the corresponding mean height for age and sex (11).

Small for gestational age (SGA) was defined as a birth weight below the 10th percentile for the gestational age, compared to a gender-specific reference population (12,13).

Growth hormone deficiency (GHD) was diagnosed when the child height was below -2 SD and or when the annual growth velocity was < -1 SD or the standing height was < −1.5 SD below the mid-parental height, in addition to a defective peak response to GH provocative testing (below 10 μg/L) associated to an insulin growth factor -1 (IGF1) level < -2 SD (14,15).

Turner syndrome (TS) was diagnosed when the X chromosome was partially or completely missing in a female (16).

All children included in the study (apart from SGA) had a normal birth weight. Among the short statured children, conventional GH provocation tests, using oral clonidine and subcutaneous glucagon, were performed to classify them as either ISS or GHD. If the magnetic resonance imaging (MRI) of hypothalamic-pituitary region was found normal in GHD children, a diagnosis of idiopathic GHD (IGHD) was made (17-21).

Based on the previous definitions, our patients were grouped into the following diagnostic categories: 154 children with GHD, 63 children with ISS, 26 children with SGA, and 9 patients with TS.

Exclusion criteria included children with systemic, metabolic or other endocrine diseases or other hormonal deficiencies (thyroxine, cortisol), insulin-dependent diabetes, chronic inflammatory and infectious disorders, anemia, and genetic syndromes (other than TS) or bone disorders.

All children included in the study had normal hemogram, renal and hepatic functions and calcium homeostasis. Circulating concentrations of free thyroxine (FT4), thyroid stimulating hormone (TSH), early morning plasma cortisol and fasting blood glucose (FBG) were normal. None of the children, included in the study, was receiving medications.

2. Methods

Before and during rhGH therapy, auxological and biochemical parameters including: height (Ht), weight (Wt), Ht-Z score (HtSDS), body mass index (BMI) and BMISDS were recorded every 6 months; bone age (BA) was assessed every 12 months. BA was evaluated using the Greulich-Pyle method, while the predicted adult height (PAH) was calculated by Bailey-Pinneau method.

Annual and total increment ratios of HtSDS were calculated over the period of full years of rhGH therapy. rhGH treatment was given at a dose 0.03 to 0.05 mg/kg/day in children with

GHD, 0.025 to 0.05 mg/kg/day to those with ISS and SGA and 0.04 to 0.06 mg/kg TS subjects. The rhGH dosage was adjusted according to the children's insulin like growth-factor 1 (IGF1) level in order to avoid levels > 2 SD (22-27).

3. Statistical analysis

Statistical analysis was performed by using SPSS, 21th edition, statistical Package. All data are expressed as mean ± SD values. ANOVA test was used to compare growth data among the 4 study groups. Paired t-test was used to compare HtSDS data after versus before rhGH treatment in each group and non-paired t test to compare HtSDS changes among different groups. Mann-Whitney *U*-test was applied to compare the differences of numerical variables between the groups at each time and chi-square test or Fisher exact test was performed to compare the frequencies between groups. Wilcoxon signed rank test was applied to compare differences of the variables within the groups at each time. A *P*-value of 0.05 or less was considered statistically significant. In multiple comparisons between all times, the Bonferroni correction was applied and a *P*-value of 0.05 or less was considered statistically significant.

Results

A total of 252 short stature children (height SDS <-2) were diagnosed and treated with rhGH in our tertiary center. The study included: 154 children with GHD, 63 with ISS, 26 with SGA, and 9 with TS. Table 1 shows the anthropometric data registered in the 4 studied groups, before rhGH treatment and at the last examination.

During the treatment period with rhGH, none of our patients with GHD, ISS and SGA had early puberty (before the age of 8 years in girls and 9 years in boys) or delayed puberty (breast development after 13 years in girls and testicular enlargement after 14 years in boys).

Before and during the treatment, all children had normal fasting BG [less than 100 mg/dL (5.6 mmol/L)] and thyroid function. Two children with GHD developed pedal edema and 3 had local allergic manifestations at the site of rhGH injection. One patient with SGA developed symptoms of high intracranial pressure (headache and vomiting) that disappeared with discontinuation of rhGH therapy. Two children complained of non-specific arthralgia that did not necessitate discontinuation of therapy.

Table 2 presents the effect of rhGH therapy in the 4 study groups and duration of their treatments. After an average of > 3 years of treatment, children with GHD increased their

HtSDS by an average of 2.2 SD. Those with TS and ISS increased their HtSDS by an average of 0.99 SD and 0.65 SD after an average of 3.5 and 7.5 years, respectively. Children with SGA increased their HtSDS by an average of 1.46, after 3.5 years of treatment.

The ANOVA test showed a significant difference in the HtSDS and BMISDS changes among the 4 groups. The bone age/chronological age (BA/CA) ratios were not significantly different between the ISS, GHD and SGA groups, after 1 and 3 years of rhGH therapy.

Table 3 compares the growth responses to rhGH therapy in GHD versus ISS groups. Both groups had significant improvement in the HtSDS after treatment with rhGH (p: < 0.01), however, the BMISDS decreased significantly in the ISS group.

Table 4 compares the growth responses to rhGH therapy in GHD versus SGA groups. Both groups had significant improvement in the HtSDS after treatment with rhGH (p: < 0.01) with no significant change in their BMISDS.

Table 1. Anthropometric data of patients with short stature

		Age 1 (year)	Ht1 (cm)	Wt 1 (kg)	Age F (year)	HtF (cm)	Wt (kg)
SGA	Mean	8.20	111.80	19.90	11.00	130.50	28.1635
	SD	3.90	19.90	10.10	3.60	19.30	12.2661
TS	Mean	9.10	112.00	27.10	16.50	141.50	51.7
	SD	3.70	16.30	12.80	4.00	9.10	16.1
ISS	Mean	11.20	127.00	27.60	14.50	143.70	39.3
	SD	4.90	14.50	10.45	3.30	29.50	13.7
GHD	Mean	10.84	125.62	28.27	14.96	146.70	44.2
	SD	4.73	17.28	11.18	4.24	35.94	17.2

Legend: Small for Gestational Age (SGA); Turner Syndrome (TS); Idiopathic Short Stature (ISS); GH Deficiency (GHD); 1 = at start of GH therapy, F = at last examination.

Table 2. Growth data before and after long-term rhGH therapy in 4 groups of short children

			Age 1 (year)	HtSDS 1	BMISDS	Age 2 (year)	HtSDS 2	Age F (year)	HtSDS - F	BMISDS- F	Delta HtSDS	Delta BMISDS
GHD	n = 154	Mean	10.84	-3.84	-0.54	11.94	(-2.77) *	14.91	(-1.63) *	(-0.23) *	2.22	0.30
		SDS	4.73	1.90	1.55	4.08	1.12	4.27	1.22	2.14	1.33	2.14
SGA	n= 26	Mean	8.19	-2.43	-0.84	9.26	-1.91	11.01	(-0.96) *	(-1.94)*	1.46	-1.14
		SDS	3.98	2.26	1.71	3.68	1.45	3.57	1.21	2.06	1.36	1.75
TS	n= 9	Mean	9.11	-3.47	0.85	10.11	-2.95	16.51	-2.49	0.99	0.99	0.13
		SDS	3.69	1.38	1.16	3.69	1.13	4.02	1.09	0.98	1.44	0.45
ISS	n= 63	Mean	11.23	-1.94	-0.33	12.13	-1.73	14.54	-1.22	(-1.73)*	0.64	-1.32
		SDS	4.87	1.44	1.95	2.62	1.02	3.33	1.66	3.26	2.42	2.94
ANOVA		P-Value	0.001	<0.00001	0.054	0.001	<0.00001	0.00004	0.003	<0.00001	<0.00001	<0.00001

Legend: Small for Gestational Age (SGA); Turner syndrome (TS); idiopathic short stature (ISS); GH deficiency (GHD); *p: <0.05 after vs before rhGH therapy. ANOVA test among 4 groups. Age 1 = at first visit, Age 2 = after 1 year of therapy, Age F = age at the last visit. HtSDS: standing height in standard deviation; BMISDS:body mass index in standard deviation.

Table 3. Comparison between growth responses to rhGH therapy in GHD versus ISS groups

			Age 1 (year)	HtSDS 1	BMISDS	Age 2 (year)	HtSDS 2	Age F (year)	HtSDS - F	BMISDS - F	Delta HtSDS	Delta BMISDS
GHD	n = 154	mean	10.84	-3.84	-0.54	11.94	-2.77	14.91	-1.63	-0.23	2.22	0.30
		SDS	4.73	1.90		4.08	1.12	4.27	1.22	2.14	1.33	2.14
ISS	n= 63	mean	11.23	(-1.93)*	-0.33	12.13	(-1.72)*	14.54	-1.22	(-1.73)*	0.63*	(-1.32)*
		SDS	4.87	1.44	1.95	2.62	1.02	3.33	1.66	3.26	2.42	2.94

Legend: Idiopathic Short Stature (ISS); GH deficiency (GHD); *p<0.05 GHD vs ISS before and after GH therapy, Age 1 = at first visit, Age 2 = after 1 year of therapy, Age F = age at the last visit, t-test: 2 samples unequal variance. HtSDS: standing height in standard deviation; BMISDS:body mass index in standard deviation.

Table 4. Comparison between growth responses to rhGH therapy in GHD versus SGA groups

			Age 1 (year)	HtSDS 1	BMISDS	Age 2 (year)	HtSDS 2	Age F (year)	HtSDS - F	BMISDS - F	Delta HtSDS	Delta BMISDS
GHD	n = 154	Mean	10.84	-3.84	-0.54	11.94	-2.77	14.91	-1.63	-0.23	2.22	0.30
		SDS	4.73	1.90	0.40	4.08	1.12	4.27	1.22	2.14	1.33	2.14
SGA	n= 26	Mean	8.19*	(-2.42)*	-0.84	(9.25)*	(-1.91)*	(11.01)*	(-0.96)*	(-1.94)*	(1.45)*	(-1.13)*
		SDS	3.98	2.26	1.71	3.68	1.45	3.57	1.21	2.06	1.36	1.75

Legend: Idiopathic Short Stature (ISS); GH deficiency (GHD);* p<0.05 GHD vs SGA before and after rhGH therapy. Age 1 = at first visit, Age 2 = after 1 year of therapy, Age F = age at the last visit, t-test: 2 samples unequal variance. HtSDS: standing height in standard deviation; BMISDS: body mass index in standard deviation.

Table 5. Comparison between growth responses to rhGH therapy in GHD versus TS groups

			Age 1 (year)	HtSDS 1	BMISDS	Age 2 (year)	HtSDS 2	Age F (year)	HtSDS -F	BMISDS - F	Delta HtSDS	Delta BMISDS
GHD	n = 154	Mean	10.84	-3.84	-0.54	11.94	-2.77	14.91	-1.63	-0.23	2.22	0.30
		SDS	4.73	1.90	1.55	4.08	1.12	4.27	1.22	2.14	1.33	2.14
TS	n= 9	Mean	9.11	-3.47	0.85*	10.11	-2.95	16.51	-2.49	0.98*	0.98*	0.13
		SDS	3.69	1.38	1.16	3.69	1.13	4.02	1.09	0.97	1.44	0.45

Legend: GH deficiency (GHD); Turner syndrome (TS); * $p<0.05$ GHD vs SGA before and after GH therapy. Age 1 = at first visit, Age 2 = after 1 year of therapy, Age F = age at the last visit, t-test: 2 samples unequal variance. HtSDS: standing height in standard deviation; BMISDS: body mass index in standard deviation.

Table 6. Growth response to rhGH therapy in GHD and ISS during the first year of therapy and at the last visit; according to the duration of GH therapy

			Age 1 (year)	HtSDS 1	BMISDS	Age 2 (year)	HtSDS 2	Age F (year)	HtSDS - F	BMISDS -F	Delta HtSDS	Delta BMISDS
GHD												
>5 years	n = 45	mean	9.22	-4.48	-0.75	10.22	-3.05	17.23	-2.22	-0.61	2.26	0.14
		SDS	4.24	1.91	1.13	4.24	1.00	4.79	1.45	2.22	1.34	2.20
<5 years	n=110	mean	11.15	(-3.66)*	-0.45	12.15	(-2.69)*	13.81	(-1.42)*	0.24	2.24	0.68
		SDS	2.94	1.82	1.68	2.94	0.90	3.05	1.03	1.43	1.43	1.54
ISS												
>5 years	n = 15	mean	10.60	-2.09	-0.54	11.60	-1.83	17.51	-1.78	-1.59	0.31	-1.05
		SDS	3.48	1.50	2.07	3.48	0.99	3.67	0.98	2.46	0.90	1.85
<5 years	n= 49	mean	11.55	-1.89	-0.47	12.55	-1.70	14.02	-1.25	-1.38	0.64	-0.78
		SDS	2.42	1.51	1.95	2.42	1.10	2.48	1.80	2.40	0.52	1.93

Legend: Idiopathic Short Stature (ISS); GH deficiency (GHD); Age 1 = at first visit, Age 2 = after 1 year of therapy, Age F = age at the last visit, t-test: 2 samples unequal variance. HtSDS: standing height in standard deviation; BMISDS: body mass index in standard deviation.

The HtSDS improvement was significantly better in GHD children versus those with TS. On long-term rhGH therapy. The BMISDS did not differ significantly in children with GHD versus those with TS (Table 5).

The HtSDS changes improvement did not differ significantly between children with GHD or ISS treated for > 5 years with rhGH versus those treated for an average of 3 years (Table 6).

Discussion

From our analyses, the following results were obtained: (a) before rhGH treatment, the GHD group had a shorter HtSDS compared to those in the ISS and SGA groups; (b) the HtSDS increments on GH therapy were higher in the GHD group compared to those in ISS and SGA groups; (c) the improvement in the HtSDS of children with ISS occurred in the first 2-3 years of therapy and did not increase furtherly by increasing the duration of treatment; (d) the HtSDS in the GHD and ISS groups showed a significant increase up-to the end of the second year of treatment, and most children had HtSDS above -2 (normal) at the end of the third year of treatment (Table 2).

In support to our results, Lee et al. (28) reported that the effect of rhGH treatment on the final height in 25 children with GHD (11 organic and 14 idiopathic) was comparable to the their target heights. Similar results, showing an improvement of HtSDS from -4.13 to + 0.22, during 3.2 years of rhGH treatment with a dosage of 0.52-0.62 IU/kg/week was reported by Choi et al. (29) in 35 children with GHD (13 idiopathic and 22 organic).

Controversy still exists about the beneficial long-term effect of rhGH treatment in children with ISS. The growth-promoting effect of rhGH appears to be variable in these children. Our study demonstrates a significant but moderate improvement of HtSDS (0.65 SD) during rhGH therapy.

This improvement occurred during the first 2 years of treatment and was significantly lower compared to GHD patients. In support to our findings, Kim et al. (30) showed that the increase in the HtSDS in children with ISS was significantly lower compared to GHD, after 1 year of treatment using the same rhGH dose.

In another study, performed in children with familial short stature treated with rhGH therapy for more than 2 years at a dose of 0.23 mg/kg/week, the final HtSDS resulted not significantly different from the control group (31).

In 3 randomized controlled trials, the increment in adult height was 0.51 SDS (3.7 cm) with a rhGH dose of 0.22 mg/kg/week, for 4.4 years (32); 0.70 SDS (4.3-5.0 cm) with GH a dose of 0.23-0.47 mg/kg/week, for 5.9 years (24), and 1.23 SDS (7.5 cm) in female with a dose of 0.42 mg/kg/week, for 6.2 years (33).

In the current study, the dose of rhGH was 0.25-0.33 mg/kg/week and the height gain, after 3 years of therapy, was 0.65 SDS. On the other hand, Kang et al. (34) reported that HtSDS in ISS children improved initially with a rhGH dose of 0.23-0.35 mg/kg/week, but HtSDS did not significantly increase, after 2 years of treatment.

Sotos and Tokar (35) subdivided their children with ISS into familial and nonfamilial groups. A more favorable final height gain was reported in the non-familial ISS group. Similar findings were reported in a Korean study of children with familial short stature (36). We did not classify our ISS children into familial and non-familial ISS groups.

Park and Cohen (37,38), in order to increase maximally the growth response to rhGH proposed a dose regimen therapy with the aim to reach initially an IGF-1 target level of +2 to +3 SDS, followed by a lower IGF-1 level during the maintenance period. In our study, we did not adopt this model of treatment and a higher rhGH dose was not recommended for safety reasons. During rhGH therapy, we readjust the doses to maintain IGF-1 levels in the upper half of the normal range (from 0 to +2 SD) for their bone age.

Our ISS children received a higher rhGH dose than that given to GHD children. However, their HtSDS improvement was less evident when compared to the GHD group. During the treatment, two children complained of non-specific arthralgia that did not necessitate the discontinuation of treatment.

Growth retardation in infancy and short stature in childhood are associated with being born SGA. About 90% of children born SGA catch up to their genetic

height potential by about two years of age. Children born prematurely may take up to four years or more to catch up and are less likely to reach adequate stature than those born at term, especially if they were small for birth length.

Genetic predisposition, intrauterine programming, decreased GH secretion, reduced sensitivity to IGF-1, and GH resistance are suggested factors that may contribute to growth failure and short stature in children born SGA (39-42).

In the United States, rhGH is approved for the treatment of short SGA children whose height remains less than 2 SD below the mean for age and sex, at two years of age (43). In Europe, the approved indication is for short SGA children whose height is less than 2.5 SD below the mean for age and sex at four years of age (44).

Our prepubertal children with SGA, treated for about 3 years with rhGH (0.03-0.05mg/kg/day), increased their HtSDS by an average of 1.46 SD [22/26 (84.6%) of children attained HtSDS >-2 after treatment]. In support to our data, Van Pareren et al. (45) carried out a randomized, double-blind, dose-response study of long-term continuous rhGH therapy in short pre-pubertal SGA (birth length < -1.88 SD) children using the adult height as the end-point. Fifty-four children were treated with a rhGH dose of 0.23 or 0.47mg/kg/week, for an average of eight years, and compared, as a control group, the short pre-pubertal SGA children not treated with rhGH. The long-term continuous therapy of short SGA children resulted in normalization of height potential, during childhood and in adult final height, in most subjects compared with non-treated controls. Eighty-five percent of children treated with rhGH had final adult heights within the normal height range and 98% were within the target heigh range.

Our SGA children, treated for 3 years with rhGH, gained 1.45 SD in their stature. In support to our data, Dahlgren et al.(46) conducted a randomized control trial in 77 short pre-pubertal children born SGA (< -2 SD in birth length or birth weight) for over 8.5 years and compared them with 34 untreated short pre-pubertal SGA children. Long-term continuous rhGH therapy at a dose of 0.23 mg/kg/week resulted in an adult height close to height predicted by the parents' stature. The shortest, lightest, and youngest children had the best response to rhGH. Children receiving rhGH therapy for more than two years, prior to puberty, gained 1.7 SD in height (~12 cm in increased adult height) compared with those treated for less than two years prior puberty, who gained only 0.9 SD in height (~ 9 cm in increased adult height). Ninety percent of their children, treated with rhGH, achieved a final adult height within 1 SD of their target height compared with 50% of the untreated children born SGA. No adverse events drug-related were observed (46).

Carel et al. (47) performed a randomized controlled study with rhGH therapy in 102 SGA children (birth length < -2 SD) who presented with short stature around puberty age (mean age =12.7 years). The treated group received a dose of 0.47 mg/kg/week and was compared with 47 untreated short peripubertal SGA controls. rhGH therapy for 2.7 years performed during puberty significantly increased the final height of short SGA children compared with untreated short SGA children group. Forty-seven percent of the rhGH-treated children had final heights in the normal range compared to 27% of the control group. The authors observed that the height gain in the treated group was directly related to rhGH therapy duration and the earlier age at the beginning of therapy.

A meta-analysis reviewed long-term trials of 391 short SGA children treated with rhGH until adult height over the past decade. rhGH treatment dose ranged between 0.23-0.47 mg/kg/week. The mean height gain from the randomized control trials was 1.5 SDS (9.5 cm) in the rhGH treated children compared to 0.25 SDS (1.6 cm) of untreated children. The mean final adult height was -0.46 SDS in rhGH-treated SGA children compared to -1.26 SDS in untreated SGA children (48,49).

On the other hand, other authors believe that rhGH treatment is likely to yield only modest gains in height compared with no treatment (an increase in final adult height of approximately 6 cm, provided the treatment is begun early and continued for at least seven years) and concluded that their adult height was below average despite therapy (50).

Many studies have noted an association between intrauterine growth restriction and long-term health

risks, including type 2 diabetes, metabolic syndrome, and cardiovascular diseases. However, the mechanisms underlying this association have not been fully established.

Our observations, during treatment with rhGH of short children born SGA, have recognized the absence of safety issues as compared with other groups of children treated with rhGH. Only one patient developed symptoms of increased intracranial pressure (early morning headache) that disappeared after discontinuation of rhGH therapy. The parents refused to restart treatment.

Patients with TS should be treated with rhGH therapy to maximize their adult height and to improve body composition. In the United States, a typical initial dose of rhGH is 0.050 mg/kg/day (0.35 to 0.375 mg/kg/week), given once daily by subcutaneous injection. Patients with TS syndrome are typically treated with somewhat higher doses of rhGH compared to patients with GHD. Growth hormone therapy should be continued until little growth potential remains (e.g. bone age exceeds 13.5 to 14 years and growth slows to less than 2.5 cm per year) (51, 52).

Our TS patients who were treated with rhGH (0.033 to 0.066 mg/kg/day) for an average of 7 years had an improvement in HtSDS of 1 SD. However, 6/9 had HtSDS < -2 at the last examination.

Sas et al. (53) evaluated rhGH therapy in 68 young girls (mean age between 6 and 7 years) with TS who were randomly assigned to three different regimens of rhGH, starting at approximately 0.045 mg/kg/day, with some groups, and escalating the dose to approximately 0.090 mg/kg/day, during the first few years of therapy. They reported a normalization of height when the treatment was started at relatively young age and with higher doses of rhGH.

Another study, which followed 60 TS subjects on long-term rhGH therapy showed that 83 percent reached a normal adult height (54). Rising the rhGH dose, over time to around 0.075 mg/kg/day, they achieved a mean additional height gain of 5.3 cm. These height outcomes were achieved after an average treatment duration of 8.6 years. Similar results were reported from an observational registry of 344 patients with TS treated with rhGH (55). Effects of very early initiation of rhGH were evaluated in a prospective, randomized, open-label clinical trial in 88 girls with TS, aged 9 months to 4 years of age. rhGH was given for two years in a dose of 0.050 mg/kg/day to 45 girls versus no treatment in 43 TS girls. The treated group increased HtSDS by 1.6 ± 0.6 SD (p: <0.0001).

These studies confirm that early rhGH therapy can correct growth failure and normalize height potentials in toddlers with TS (56-59). A beneficial effect on bone growth and body composition with increased lean body mass and decreased body fat has been also reported (57-59). In our patients with TS, the BMIS-DS did not show any significant change during rhGH therapy. Furthermore, rhGH treatment does not appear to have a deleterious effect on blood pressure, left ventricular function, or aortic diameter. None of our TS patients had any of the side effects related to rhGH therapy, including slipped capital femoral epiphyses, intracranial hypertension, and pancreatitis (60).

In conclusion, children with SGA, ISS and TS groups showed significant increases in HtSDS when treated with rhGH for 2 to 3 years. However, their HtSDS increments were significantly lower than those attained in children with GHD. No deleterious side effects requiring cessation of therapy were registered in the majority of our children.

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Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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