CLINICAL STUDY

Treatment of tall stature in boys with somatostatin analogue 201-995: effect on final height

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Abstract

Background: An optimal treatment for tall stature in boys in terms of efficacy and safety is not available. Treatment with somatostatin analogue 201–995 (SMS) has been tried with positive short-term results.

Methods: We evaluated the effect of SMS treatment on reducing adult height. Over 2 years, 16 boys presenting to our university hospital with tall stature (constitutional tall stature ($n = 13$), Marfan syndrome ($n = 2$) and tethered spinal cord ($n = 1$)) with a predicted final height above 197 cm were included in the study and prospectively followed until final height was reached. As one boy was lost to follow-up we have reported on 15 boys. Treatment with SMS as a single subcutaneous dose was started and continued until final height was reached. In eight boys androgens were given to induce puberty after the start of SMS and five boys were on treatment with androgens prior to SMS treatment. Effect on reduction of final height prediction, calculated with the index of potential height based on the bone age of Greulich and Pyle, was the main outcome measure. Standard anthropometric assessments were performed a year before and every 3 months during treatment. Bone age was assessed by the method of Greulich and Pyle at the start and after 6 and 12 months.

Results: Mean reduction in final height prediction (predicted adult height minus achieved adult height) was -0.1 cm (range -6.4 to $+5.7$). In three boys, asymptomatic microlithiasis of the gall bladder was diagnosed.

Conclusions: We have concluded that, in spite of encouraging short-term results, long-term treatment with SMS does not reduce final height in a manner sufficient to justify SMS treatment in tall stature.

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Introduction

High doses of sex steroids are still the conventional treatment for tall stature in boys (1–3). However, long-term side-effects are difficult to assess and are still not clear (4–6). The window for therapy is limited to puberty but results are best if therapy is started at an early age (7). There is a need for a growth-reducing therapy without inducing premature or early puberty. Somatostatin could potentially offer this. Somatostatin is a neuropeptide produced at the hypothalamic level that has potent inhibitory properties on growth hormone (GH) release in the pituitary via the vascular network of the portal system (8). Furthermore, it is hypothesized that the somatostatin analogue 201–995 (SMS) has local regulatory effects on bone growth and metabolism (9–10). Several groups have reported on the role of SMS for the management of tall stature with a beneficial reduction in short-term growth in a number of

children (11–13). Long-term effects of SMS therapy on growth velocity and final height are not available however. We report our experience of treatment with SMS for tall stature and the effect of SMS on final height.

Patients and methods

We have studied the effect of SMS (Novartis, Arnhem, The Netherlands) on growth in 15 tall boys. Eligible for the study were boys with predicted adult height (PAH) according to the Bayley & Pinneau (14) method above 197 cm who presented in our clinic in the period between June 1993 and June 1995 (7). Of the 16 boys, one was lost to follow-up after 1 year and was not included in the analysis. In the remaining 15 boys the diagnosis was constitutional tall stature (CTS) in 12 and Marfan syndrome in two boys. One boy had a tethered spinal cord (TSC) and a PAH of

189 cm and was treated to diminish growth and aggravation of neurological symptoms due to the TSC. The karyotype in all boys was 46 XY.

Standard anthropometric assessments were performed a year before and at three-monthly intervals during therapy. Final height was registered if the height increment was less than 0.5 cm in the preceding year. Pubertal stages were scored every visit according to the standards of Tanner & Whitehouse (15). Bone age (BA) was assessed by the method of Greulich & Pyle (GP) (16) by two experienced observers (C N and B J O). Height was expressed in standard deviation scores (SDS) compared with Dutch standards (17). PAH was calculated using the index of potential height based on BA readings according to the method of GP (IPHGP) and the BP method (7). Free thyroxine and insulin-like growth factor (IGF)-I were measured every 6 months initially and later yearly. GH secretion was monitored before and after the start of SMS treatment.

The boys or their parents administered subcutaneous SMS injections as a single dose in the evening. Starting dosage was 0.05 mg SMS in prepubertal boys and 0.15 mg in pubertal boys. In cases where GH secretion and/or height velocity (HV) did not decrease by more than 50% we increased the SMS dosage to a maximum of 0.15 mg in prepubertal boys and 0.25 mg in pubertal boys. It was not possible to increase the SMS dosage in some of the boys because of side-effects.

In eight patients, androgens were given to induce puberty after the start of SMS treatment (mean interval 18 months, range 6–30 months). Five boys were on treatment with androgens prior to SMS treatment (mean duration of treatment 17 months, range 12–21 months) in order to reduce final height. The decision to start androgen treatment was made on clinical grounds by the two clinicians (C N and B O). To analyse the results properly the boys were divided into two groups. Group 1 ($n = 10$) received only SMS treatment or started androgens after 6 months or 12 months of SMS therapy. For the analysis of HV only the period without androgen treatment was considered. Group 2 ($n = 5$) received androgens prior to SMS treatment. The clinical characteristics of the boys are given in Table 1.

Overnight studies of GH secretion were performed in nine boys. Twelve-hour overnight GH profiles were performed prior to the start in the nine boys, after 1 day of SMS treatment in four of the nine boys and after 3 months of SMS treatment in five of the nine boys. For GH studies, children were admitted to the hospital in the morning and allowed normal activities during the day. At 1900 h an indwelling catheter was placed in a vein and connected to a constant withdrawal pump (Conflo; Carmeda AB, Stockholm, Sweden). Tubes containing heparin were changed every 20 min in the period from 2000 to 0800 h and were kept on ice before measurement of plasma GH.

Table 1 Clinical characteristics of 15 boys treated with SMS at the start of treatment.

No.	Diagnosis	CA (years)	BA (years)	Pubertal stage	Height (cm)	Height SDS (IPHGP)	PAH (IPHGP)	SMS treatment (months)	SMS dosage (mg; min–max)	Start of androgens (months)	Androgen treatment (testosterone propionate)
1	CTS	13.3	14.3	5	191.8	4.1	199.8	20	0.2–0.2	–	–
2	TSC	10.8	11.5	1	154.6	1.4	187.1	60	0.05–0.2	–	–
3	CTS	12.1	13.5	3	187.7	5.0	203.5	24	0.1–0.2	+6	100 mg/3 weeks → 250 mg/3 weeks
4	CTS	12.9	13.3	2	181.8	3.3	201.2	15	0.05–0.2	+6	50 mg/4 weeks → 100 mg/4 weeks
5	CTS	11.8	13	2	172.1	3.3	195.0	21	0.05–0.15	+9	100 mg/3 weeks → 250 mg/2 weeks
6	CTS	12.3	13	2	179.9	3.6	202.0	36	0.1–0.2	+12	250 mg/2 weeks → 250 mg/week
7	CTS	8.5	9.5	1	158.2	4.7	203.3	66	0.05–0.2	+31	100 mg/3 weeks → 250 mg/2 weeks
8	CTS	8.8	10.5	1	157.5	4.3	195.7	60	0.05–0.2	+30	100 mg/2 weeks → 250 mg/3 weeks
9	Marfan	10.5	11.5	1	164.1	3.1	197.1	52	0.1–0.2	+21	50 mg/3 weeks
10	Marfan	9.5	11.5	1	158.4	3.2	191.1	52	0.1–0.2	+30	100 mg/3 weeks → 250 mg/3 weeks
Mean (group 1)		11.1	12.2					41		+18	
11	CTS	12.8	13.5	4	197.4	4.9	211.4	30	0.05–0.25	–18	50 mg/3 weeks → 250 mg/2 weeks
12	CTS	14.5	14.5	5	198.8	3.4	203.5	15	0.1–0.1	–21	50 mg/2 weeks → 250 mg/week
13	CTS	14.9	15.5	5	199.9	3.4	202.5	15	0.05–0.05	–20	100 mg/3 weeks → 250 mg/week
14	CTS	15.8	15.5	5	192.5	1.9	196.3	12	0.2–0.2	–14	250 mg/2 weeks
15	CTS	15.8	14.5	5	197.8	2.6	202.8	15	0.1–0.2	–12	250 mg/3 weeks → 250 mg/week
Mean (group 2)		14.8	14.7					17		–17	
Mean (total)		12.3	13.0					33			

CA, calendar age; BA, bone age; SDS, standard deviation score; Marfan, Marfan syndrome; start of androgens, +, before start of SMS treatment, –, after start of SMS treatment.

Informed consent was given by the parents and the boys, when applicable.

Hormone assays

Plasma GH concentrations were measured by direct RIA using the international WHO standard for human GH 80/505. The interassay coefficients of variation (CV) were 9.2, 7.8, 5.0 and 6.0% at GH concentrations of 4.7, 10.6, 20.8 and 53.5 mU/l. The intra-assay CV, expressed as the relative duplicate variation of samples with a GH concentration between 1.0 and 60 mU/l ($n = 40$), was 5.1%. The lower limit of detection was 0.2 mU/l.

IGF-I was determined by an in-house RIA following acidification and silica C-18 extraction of the plasma samples. The bound and free proteins were separated using a solid-phase second antibody-coated cellulose suspension. The rabbit antiserum used in this assay showed negligible cross-reactivity with IGF-II. The intra-assay CV, expressed as the relative duplicate CV at concentrations between 5 and 50 nmol/l, was 5.7%. The interassay CV was 9.4% at a level of 8.4 nmol/l, 4.1% at 29.8 nmol/l and 6.5% at an IGF-I concentration of 41.7 nmol/l. The sensitivity of the assay was 7 pmol/l. IGF-I levels were expressed as SDS values for BA using our normative data (authors' unpublished data).

Analysis of 12-h overnight GH profiles

The GH data were analyzed using the Pulsar program version 2.0 (Meriam & Wachter (18)). $G(n)$ values were set as $G(1) = 5$, $G(2) = 3$, $G(3) = 2$, $G(4) = 1.5$ and $G(5) = 1$. The peak splitting cut-off level was set at 2.7 and weight assigned to peaks at 0.05. The mean GH value was derived from the program.

The 95% concentration interval (CI) of mean GH levels for 12-h overnight GH profiles was obtained using the method of Rose *et al.* (19) for comparing mean GH levels. To apply the normal values for data obtained with our GH assay we exchanged samples between our

laboratory and Hazleton Washington Laboratories (Vienna, VA). A regression curve was subsequently constructed and the 95% CI of the normal values was recalculated for our assay. The 95% CI for the mean overnight GH level for our assay is 6.5–21.2 (mean 10.5) mU/l for prepubertal boys below 9 years and 6.5–23.3 (mean 10.8) mU/l for prepubertal boys over 9 years. For pubertal boys, the mean overnight GH levels ranged from 11.6 mU/l (Tanner stage 2) to 17.2 mU/l (Tanner stage 4). Mean GH levels are expressed as SDS values for age and Tanner stage using these normal values.

Statistics

The differences between PAH and achieved adult height were tested with the Wilcoxon signed ranks test.

Results

The mean age of the 15 boys was 12.3 years (range 8.5–15.8). The mean duration of SMS treatment was 33 months (range 12–66 months).

Short-term effect

Table 2 shows the HV during the first year of treatment in the boys without androgen treatment. In all but one, HV decreased after the start of treatment. During the first year of SMS treatment, bone maturation was retarded (BA/calendar age (CA) < 1) in half of the boys in whom this could be evaluated.

Long-term effect

Effect of SMS treatment on reduction of final height is shown in Table 3. At final height, the mean effect of treatment (i.e. predicted adult height minus achieved adult height) according to the IPHGP in group 1 was -0.8 cm (range -6.4 to $+5.7$ cm). The mean change in group 2 was $+1.4$ cm (range $+0.3$ to $+1.6$ cm). According to BP the mean change in group 1 was

Table 2 Evolution of HV and bone maturation during 6 and 12 months of SMS treatment in the boys without androgen treatment.

No.	HV before SMS (cm/year)	HV over 6 months of SMS (cm/year)	HV over 12 months of SMS (cm/year)	Bone maturation over 6 months of SMS (Δ BA/ Δ CA)	Bone maturation over 12 months of SMS (Δ BA/ Δ CA)
1	na	8.2	6.8	0.5	1
2	7.8	3.6	3.5	0.5	1
3	8	7.8	—	2	—
4	6.8	5	—	1	—
5	7.2	3.7	—	1	—
6	11	7.8	8.2	1	1.3
7	10.4	6	5	0.5	0.5
8	8.4	6.2	5.8	0.5	0.5
9	5.6	4.6	5.5	0.5	0.5
10	5.8	6.4	6	1	0.8
Mean (group)	7.9	5.7	5.7		

Δ , change; na, not available.

Table 3 Effect of treatment according to IPHGP and BP.

No.	PAH IPHGP (cm)	PAH BP (cm)	Final height (cm)	Effect of treatment (IPHGP) (cm)	Effect of treatment (BP) (cm)
1	199.8	204.5	201.9	-2.1	+2.6
2	187.1	189.0	184.9	+2.2	+4.1
3	203.5	214.5	209.9	-6.4	+4.6
4	201.2	204.3	205.0	-3.8	-0.7
5	195.0	202.5	192.7	+2.3	+9.8
6	202.0	205.4	198.6	+3.4	+6.8
7	203.3	205.7	197.6	+5.7	+8.1
8	195.7	207.8	197.6	-1.9	+10.2
9	197.1	200.6	197.2	-0.1	+3.4
10	191.1	198.1	198.1	-7	0
Mean (group 1)	197.6	203.2	198.4	-0.8	+4.9
11	211.4	218.8	209.1	+2.3	+9.7
12	203.5	209.7	203	+0.5	+6.7
13	202.5	204.8	200.9	+1.6	+3.9
14	196.3	197.2	196	+0.3	+1.2
15	202.8	203.0	200.5	+2.3	+2.5
Mean (group 2)	203.3	206.7	201.9	+1.4	+5.4
Mean (total)	199.5 ^b	204.4 ^a	199.5 ^{a,b}	-0.1	+5.0

Effect of treatment, predicted adult height minus achieved adult height.

^asignificant difference ($P = 0.001$) (Wilcoxon signed ranks test); ^bno significant difference

+4.9 cm (range -0.7 to +10.2 cm) and in group 2 it was +5.4 cm (range +1.2 to +9.7 cm). For all boys together, the mean change according to BP was significant. All patients in group 2 showed a reduction in final height.

Endocrinology

In the 12-h GH profiles, mean GH level showed a wide range of values with levels clearly in the normal range to levels less than -2 s.d. below the mean for age and Tanner stage. Mean GH level was 9.5 mE/l (range 2.3-20.1) ($n = 9$) just before the start of SMS treatment and 4.7 mE/l (range 0.2-10.0) ($n = 9$) during SMS treatment. Mean GH level expressed as SDS values for Tanner stage was -1.2 (range -3.9 to +1.2) before the start of treatment. At the second observation in four boys after 1 day of SMS treatment, mean GH level SDS was -3.3 and in five boys after 3 months (104-115 days) mean GH level SDS was -3.6.

Mean IGF-I SDS was +0.4 (range -1.1 to +3.9) at the start of treatment. After 6 months the mean IGF-I SDS was -1.1 (range -2.1 to +1.9) and after 24 months of treatment -1.0 (range -2.1 to +2.0). Serum free thyroxine concentration decreased in all but one. Mean free thyroxine level decreased from 12.4 pmol/l to 8.6 pmol/l after 1 year and to 9.9 pmol/l after 2 years of SMS treatment (normal values 8-22 pmol/l). None of the boys developed hypothyroidism during treatment. After discontinuation of SMS treatment free thyroxine returned to pretreatment levels (11.3 pmol/l).

Side-effects

SMS was fairly well tolerated, no patient discontinued treatment because of side-effects. Transient diarrhoea

was noted as well as initial abdominal discomfort in six of the 15 boys. Asymptomatic microlithiasis of the gall bladder was diagnosed in three boys.

Discussion

These data demonstrate that SMS treatment reduces the HV of tall boys in the first 12 months of treatment, confirming previous reports (11-13). The effect on adult height is less evident. Of course the effect depends upon the method that is used to predict adult height. BP prediction tends to overpredict and IPHGP tends to underpredict but is the most reliable in predicting adult height (7). Taking this into account, the mean effect of our height-reductive treatment in these boys was limited to a few centimetres. As in these boys the mean BA was 13 years the effect was smaller than the effect of 'conventional' androgen treatment (7).

Our data are the first reporting on long-term SMS treatment and its effect on adult height. Hindmarsh *et al.* (12) reported on final height after 2 years of SMS treatment in five patients. The data are in line with our data showing a variable effect of SMS treatment of a limited magnitude. They suggested that the effect was better in younger children and in our study the younger children also did better. One has to realize, however, that in the younger children treatment was given over 5 years as it was continued until final height. We did not terminate treatment at the start of puberty as has been suggested by others (12).

We found a clear heterogeneity of GH secretion, with some even having low GH secretion; this has already been reported (20). Although we made a limited number of observations, mean GH levels clearly

decreased in the very short run, an effect that was apparently sustained over 3 months. Follow-up of IGF-I levels showed a decrease that was sustained over 2 years of treatment. Given the baseline mean GH levels, the clearly negative effect of SMS on mean GH and IGF-I levels, and the limited effect of SMS on reducing final height, GH action seems less important in the 'pathogenesis' of constitutional tall stature.

We did not observe accelerated bone maturation as reported by Tauber *et al.* (11) who treated ten pubertal adolescents with a high dose of SMS. We found a sustained and reversible effect on free thyroxine levels as expected in treatment with SMS and reported previously with suppression of TSH levels by SMS (21). The magnitude of the changes was limited so we can hardly believe that these changes in thyroid function contributed to the retarded bone maturation in some of the boys.

A limitation of this study was that the treatment regimens in the boys were variable. However, we always tried to increase the SMS dosage under the guidance of HV and/or GH secretion. Sometimes this was not possible because of the, in our opinion considerable, frequent side-effects. In cases where pubertal progress was slow, additional androgen treatment was given in an identical way. We therefore suggest that these data provide a valuable insight into the effect of SMS treatment on adult height in tall boys. Given the range of observations (ages and strategies) that we made we consider there is no treatment strategy with SMS that 'works'.

We conclude that, in spite of encouraging short-term results, long-term treatment with SMS does not reduce final height in a manner sufficient to justify SMS treatment in tall stature.

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