

# Growth Hormone Therapy in Turner's Syndrome: One Versus Two Daily Injections\*

JEAN DE SCHEPPER, MARGARETHA CRAEN, GUY MASSA,  
CLAUDINE HEINRICHS, MARC MAES, MARC DU CAJU, LEON RAUSIN,  
AND JEAN-PIERRE BOURGUIGNON

*Divisions of Pediatric Endocrinology, Departments of Pediatrics, Universities of Brussels, Leuven, Louvain, Antwerp, Ghent, and Liege, Belgium*

## ABSTRACT

In 44 girls with Turner's syndrome, aged 4.0–15.3 yr, the effects of biosynthetic GH (25 U/m<sup>2</sup>·week) given as once daily or twice daily injections were compared. During 1 yr of treatment, the growth rate increased similarly by 3.5 ± 1.3 cm/yr in the once daily group and 2.7 ± 1.8 cm/yr in the twice daily group. Although pretreatment height velocity was negatively related to age, the increase in height velocity during therapy was not. The mean progression in bone age (TW2-RUS method) during therapy was 1.3 yr in both groups. No significant change in the median insulin secretory response to an oral glucose

tolerance test was found. Serum cholesterol and triglyceride concentrations did not change significantly throughout the study in either treatment group. Thyroid hormone concentrations remained within normal limits. Normal increments in left ventricular wall thickness and left ventricular mass for age and body surface were observed after 1 yr of GH treatment. We conclude that division of the daily GH dose given to Turner's syndrome patients into two injections does not result in either a significantly different growth response or different side-effects from once daily treatment during the first year of therapy. (*J Clin Endocrinol Metab* 79: 489–494, 1994)

SINCE 1960, GH has been used in patients with Turner's syndrome (TS) in an attempt to increase growth rate and final height (1). Although conventional replacement doses were not effective, supraphysiological doses between 24–30 U/m<sup>2</sup>·week resulted in a significant increase in height velocity for several years (2–8). In addition, single daily administration of GH induced a greater growth response than three injections per week (9). It was not known, however, whether a higher frequency of GH administration in these patients could account for a further increase in growth response.

The possible long term side-effects of high dosages of GH are a matter of concern in TS patients (10). Of particular importance is the influence of GH on glucose tolerance, lipid profile, thyroid function, blood pressure, and cardiac function, because TS patients are at increased risk for developing diabetes mellitus, obesity with secondary hyperlipidemia, autoimmune thyroiditis, hypertension, and other cardiovascular complications (11–16). In this respect, a twice daily injection regimen, accounting for lower peak GH concentrations, might have different consequences than single daily injections. Therefore, a study of efficacy and safety was set up in TS patients receiving GH as once (OD) or twice (TD) daily injections. Here we report the effects on linear growth, bone maturation, insulin secretion, blood lipid profile, as

well as thyroid and cardiac function after 1 yr of GH treatment.

## Subjects and Methods

Forty-four girls with TS followed in 7 university medical centers were entered into the study. At the onset of GH therapy, their chronological age ranged from 4–15.3 yr, and their bone age ranged from 3–13.1 yr. All had a pretreatment height velocity within 2 SD of the mean for TS-specific growth standards (17). The karyotype was 45,XO in 24 patients, whereas structural X aberrations or mosaicism were found in 20, including 4 patients with XO/XY mosaicism, in whom gonadal remnants had been surgically removed at least 1 yr before treatment. At entry, none of the patients showed breast development, whereas pubic hair (Tanner stage 2–3) was observed in 7 girls.

Written consent was obtained from the parents. The study protocol was approved by the ethical committee of the participating centers.

The patients were randomized to receive 25 U/m<sup>2</sup>·week biosynthetic GH (Norditropin, Novo-Nordisk, Copenhagen, Denmark) in either one (OD group) or two (BID group) daily injections. In the randomization process, pretreatment growth rate, chronological age, parental height, and karyotype were taken into account (Table 1). GH was administered sc using a commercial pen injection system (Nordiject, Novo-Nordisk). The calculated doses were rounded to the nearest 0.25 U and adjusted to body surface every 6 months. The daily dose of GH was administered as an evening injection in the OD group, whereas it was divided into two equal injections (morning and evening) in the BID group. No sex steroids were administered during the study period.

Height, weight, pubertal stage, and blood pressure were assessed at the start of the study and every 3 months subsequently. Height was measured using a Harpenden stadiometer, and the mean value of three estimates was calculated. The SD scores (SDS) of height and height velocities were calculated with reference to the data of Tanner *et al.* for normal children (18) and the data of Ranke *et al.* for TS patients (17). Body mass index (BMI; weight/height<sup>2</sup>) was calculated and compared with the age- and gender-specific data of Rolland-Cachera *et al.* (19). The stages of pubertal development were assessed according to Tanner (20). Blood pressure was measured with a mercury sphygmomanometer.

At the start of treatment and after 12 months, bone age (TW2-RUS method) (21) was determined by a single pediatric radiologist, using an x-ray of the left hand and wrist. Fasting glucose, insulin, cholesterol,

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Address all correspondence and requests for reprints to: Dr. J. De Schepper, M.D., Division of Pediatric Endocrinology, Department of Pediatrics, Academic Hospital VUB, Laarbeeklaan 101, B-1090 Brussels, Belgium.

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**TABLE 1.** Data of TS patients at the start of GH therapy, given as one or two daily injections

	1 daily injection (n = 22)	2 daily injections (n = 22)
Age (yr)	8.8 ± 3.8	9.1 ± 3.6
Ht (cm)	114.0 ± 18.0	116.6 ± 16.3
Ht SDS (for normal girls) <sup>a</sup>	-2.78 ± 0.94	-2.61 ± 0.97
Ht SDS (for TS girls) <sup>b</sup>	0.09 ± 0.91	0.32 ± 0.82
Wt (kg)	24.2 ± 11.6	25.1 ± 10.2
BMI SDS (for normal girls) <sup>c</sup>	0.42 ± 1.28	0.52 ± 1.28
Ht velocity (cm/yr)	4.65 ± 1.48	4.70 ± 1.4
Ht velocity SDS	0.38 ± 0.76	0.61 ± 0.86
Midparental ht (cm)	166.9 ± 6.2	167.5 ± 6.7
Bone age (yr)	7.8 ± 3.6	8.3 ± 3.0
Karyotype (n)		
45,X0	11	13
Others	11	9

Data are the mean ± SD.

<sup>a</sup> Standards of Tanner *et al.* (18).

<sup>b</sup> Standards of Ranke *et al.* (17).

<sup>c</sup> Standards of Rolland-Cachera *et al.* (19).

and triglyceride were measured at the start and after 1 yr of treatment. A standard oral glucose tolerance test (OGTT; 1.75 g glucose/kg, up to 75 g) was performed in 41 patients before therapy and after 1 yr (at least 48 h after the last GH injection). The integrated glucose and insulin concentrations were calculated according to the formula: area, 0.25 (fasting value) + 0.5 (30 min value) + 0.75 (60 min value) + 0.5 (120 min value) (22). The standards from the National Diabetes Data Group for children were used to define impaired glucose tolerance (23). In the analysis of OGTT results after 1 yr of therapy, the data from three patients were excluded because they received the last GH injection less than 48 h before the test. Thyroid function and glycosylated hemoglobin (HbA<sub>1c</sub>) were measured every 3 months. These measurements were performed in the laboratory of each center; all centers participated in a national quality control program to ensure the comparability of assay results.

In 38 patients (19 in each treatment group), standard M-mode echocardiography was performed at the start of GH treatment and after 1 yr. Measurements were made according to the recommendations of the American Society of Echocardiography (24). The left ventricle data were compared to the references from Henry *et al.* (25). The left ventricle mass was calculated according to the method of Devereux *et al.* (26). The left ventricular shortening fraction was computed by taking the difference between the end diastolic and systolic dimensions divided by the end diastolic dimension.

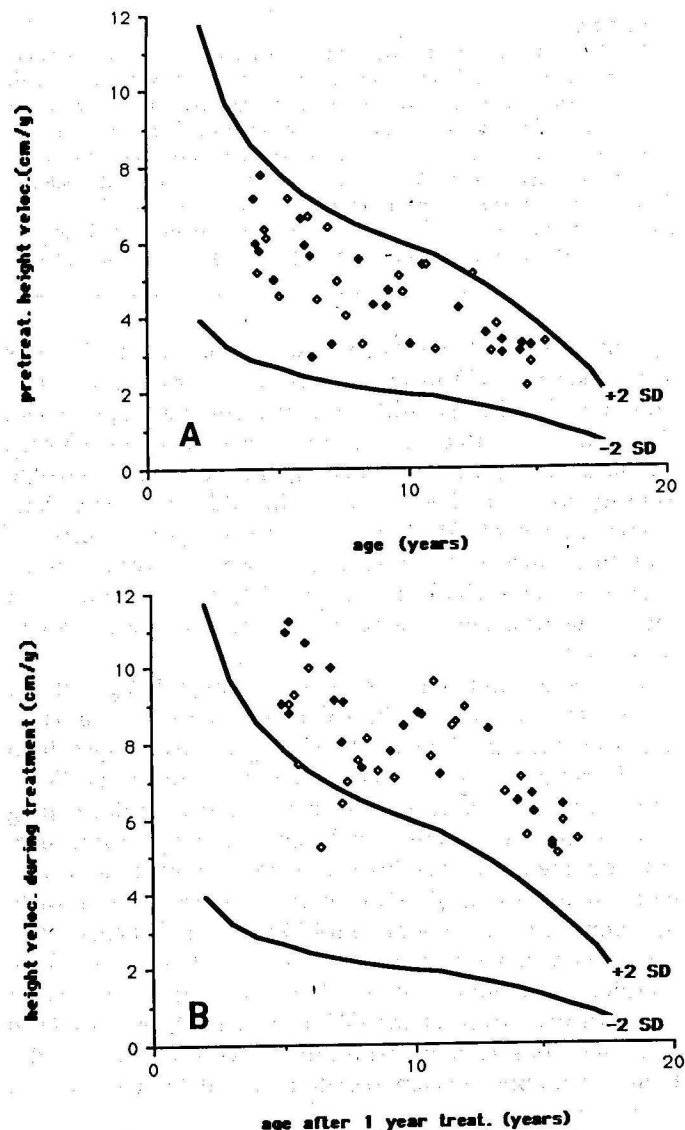
Auxological data from the two treatment groups were compared at baseline using the unpaired Student's *t* test. Analysis of variance for repeated measurements was used to calculate the significance of changes with time and treatment regimen and/or interaction of time with the treatment schedule. The biochemical parameters, which were not normally distributed, were compared between the two treatment groups by the Mann-Whitney U test and the Wilcoxon rank test for measurements within each group. The correlation between various data was calculated by regression analysis. The level of significance was set at  $P < 0.05$ .

## Results

### Auxological data

During 1 yr of GH treatment, the mean height velocity ( $\pm$ SD) increased significantly in both groups, from  $4.6 \pm 1.5$  to  $8.2 \pm 1.7$  cm/yr in the OD group and from  $4.7 \pm 1.4$  to  $7.4 \pm 1.5$  cm/yr in the BID group. The mean change in height velocity was not significantly different in the two groups ( $3.5 \pm 1.3$  cm/yr in the OD group and  $2.7 \pm 1.8$  cm/yr in the BID group). In the entire group of patients, the mean height SDS (for TS) rose from  $0.20 \pm 0.86$  to  $0.92 \pm 0.85$  ( $P < 0.001$ ). Height velocity above 2 SD for TS patients was obtained in

42 of 44 treated patients. For unclear reasons, two patients showed unchanged or reduced height velocity during therapy. It is possible that the pretreatment height velocity was overestimated in at least one of them. As shown in Fig. 1, A and B, height velocity before and during treatment was negatively related to age ( $r = -0.74$  and  $-0.68$ , respectively;  $P < 0.001$ ). In contrast, the change in height velocity during treatment was not correlated with age at the start of treatment (Fig. 2). When expressed as SDS for TS, height velocity and the change in height velocity during the first year of treatment were positively correlated with age at the start of treatment ( $r = 0.63$ ;  $P < 0.001$  and  $r = 0.50$ ;  $P < 0.001$ ). However, these data may be biased by the important reduc-



**FIG. 1.** A, Pretreatment height velocity in relation to age at start of GH treatment in patients with TS (■; patients with one daily injection; □, patients with two daily injections). —, The limits (+ and -2 SD) of height velocity in untreated TS girls (17). B, Height velocity during treatment in relation to age after 1 yr of GH treatment in patients with TS (■, patients with one daily injection; □, patients with two daily injections). —, The limits (+ and -2 SD) of height velocity in untreated TS girls (17).

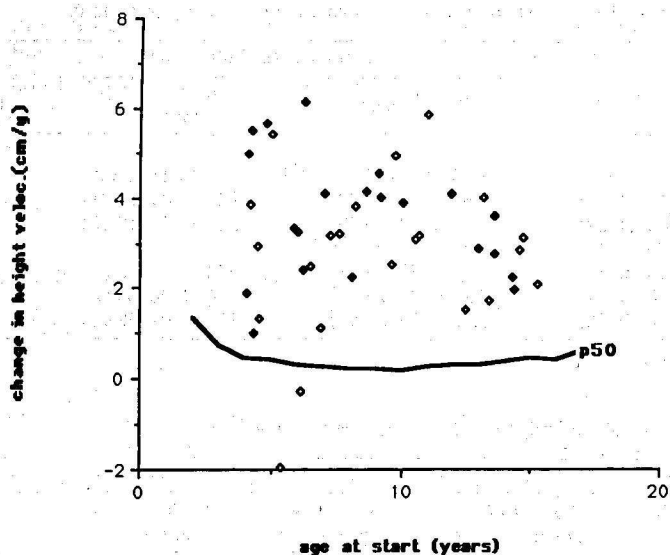


FIG. 2. Change in height velocity during the first year of GH treatment in relation to age at the start of treatment (■, patients with one daily injection; □, patients with two daily injections). —, The 50th percentile of change in height velocity in relation to age in untreated TS girls (17).

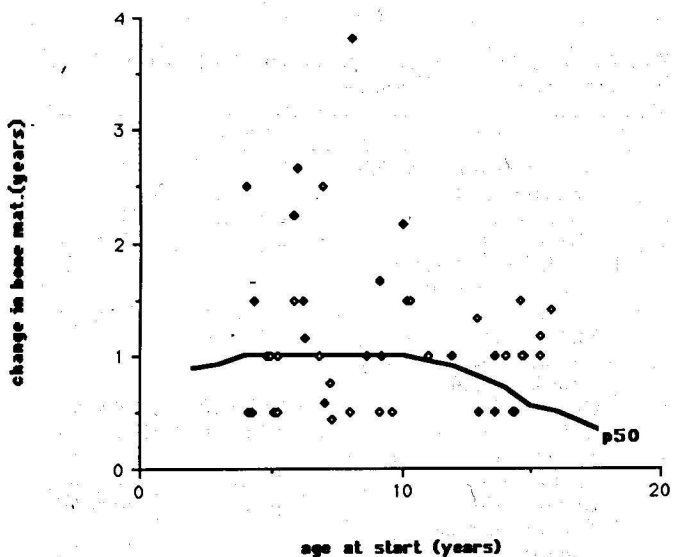


FIG. 3. Change in bone maturation during the first year of GH treatment in relation to age at the start of the treatment (■, patients with one daily injection; □, patients with two daily injections). —, The 50th percentile of change in bone maturation in relation to age in untreated TS girls (17).

tion in the magnitude of the SD in height velocity with age. The increase in height velocity was not related to either karyotype or midparental height.

During therapy, mean bone age (TW2-RUS method) increased from  $7.8 \pm 3.6$  to  $9.1 \pm 2.9$  yr (mean increment,  $1.3 \pm 0.6$  yr) in the OD group. In the BID group, a similar change in skeletal maturation from  $8.3 \pm 3.0$  to  $9.6 \pm 2.5$  yr (mean increment,  $1.3 \pm 0.5$  yr) was observed. As shown in Fig. 3, in most patients, the change in bone maturation during therapy was greater than the mean maximum change in bone age/maximum change in chronological age ( $\Delta BA/\Delta CA$ ) for

untreated TS patients. This was more obvious in the younger patients, because  $\Delta BA/\Delta CA$  was negatively correlated ( $r = -0.51$ ;  $P < 0.001$ ) to age at the start of treatment.

#### Carbohydrate and lipid metabolism

In all the patients, the fasting plasma glucose concentration was normal before treatment and after 12 months. Before therapy, the median fasting plasma glucose concentration and median integrated glucose levels during OGTT were similar in both groups (Table 2). Five of 41 patients showed impaired glucose tolerance before treatment (4 in the OD group and 1 in the BID group). After 1 yr of therapy, glucose tolerance evaluated at least 48 h after the last GH injection (38 of 41 patients) was normal in all patients. The median peak level of glucose and the area under the curve of the glucose response after 12 months of treatment were not significantly different from pretreatment data in either treatment group.

The median fasting serum insulin concentration and peak insulin response to OGTT were not significantly different in the two groups before as well as after GH therapy. As shown in Table 2, insulin secretion after an oral glucose load was slightly increased after 12 months of treatment in the OD group, whereas in the BID group, a slight decrease in median insulin output was observed. However, these changes were not significantly different because of the great individual variations in insulin response in both groups. Changes in weight, BMI, or height velocity could not explain the variations in insulin secretion after 1 yr. No difference in the insulin response was found between the patients with 45,XO karyotype and those with other chromosomal abnormalities. In the three patients who received the last GH injection 24 h before the OGTT, the insulin response was more than double the pretreatment value (data not shown). At the start of GH treatment, the mean  $HbA_{1c}$  concentration was within the reference range. During treatment, similar data were observed in both groups (Table 3). An abnormally elevated  $HbA_{1c}$  value (8.4%) was transiently observed in one patient who responded normally to OGTT on both occasions.

Before treatment, an elevated fasting cholesterol concentration ( $>5.18$  mmol/L) was found in seven patients, and an elevated triglyceride concentration ( $>1.69$  mmol/L) in one patient. There was no difference in the mean concentrations of these analytes in the two groups. After 1 yr of GH treatment, no change in mean cholesterol concentration was seen, whereas the mean triglyceride concentration showed a slight, though not significant, increase (14%). The increase in triglyceride concentration was not related to age, change in BMI, or change in insulin secretion during therapy.

#### Thyroid function

Thyroid function tests were within normal limits at the start of treatment in all patients, whereas thyroid autoantibodies were detectable in four patients. As no significant differences in thyroid function parameters were found between the two treatment regimens, the data from the two groups were pooled. As shown in Table 3, a significant and transient increase (17%) in the mean serum  $T_3$  concentration was seen after 3 months of GH therapy. Mean serum con-

**TABLE 2.** Glucose and insulin concentrations in TS patients before and after 1 yr of GH treatment, given as one or two daily injections

	OD group (n = 18)		BID group (n = 20)	
	Pretreatment	After 1 yr of GH therapy	Pretreatment	After 1 yr of GH therapy
Glucose				
Basal conc. (mmol/L)	4.38 (3.08–5.45)	4.24 (3.37–5.06)	4.43 (3.69–6.72)	4.35 (3.41–6.66)
Peak conc. (mmol/L)	7.65 (5.62–13.77)	7.99 (6.11–12.56)	7.87 (5.95–12.72)	7.16 (5.84–10.91)
AUC (mmol/L·min)	12.28 (10.91–21.32)	12.83 (9.86–20.27)	13.5 (8.92–20.55)	12.06 (8.76–16.75)
Insulin				
Basal conc. (pmol/L)	1.11 (0.07–1.81)	0.97 (0.13–3.06)	1.18 (0.55–2.36)	1.11 (0.55–3.20)
Peak conc. (pmol/L)	4.80 (2.23–21.04)	7.10 (3.76–33.31)	7.10 (3.62–23.83)	6.82 (3.06–35.95)
AUC (pmol/L·min)	6.69 (2.50–20.90)	9.75 (5.15–44.73)	10.73 (4.73–36.23)	8.36 (5.01–59.23)

Data are the median and range (in parentheses). AUC, Area under the curve.

**TABLE 3.** Serum concentrations of HbA<sub>1c</sub>, thyroid hormones, TSH, cholesterol, and triglyceride during GH treatment

	0 months	3 months	6 months	9 months	12 months
HbA <sub>1c</sub> (%)	5.29 ± 1.02	5.07 ± 0.93	4.95 ± 0.77	5.38 ± 0.79	4.86 ± 0.90
T <sub>4</sub> (nmol/L)	116 ± 19	115 ± 17	114 ± 21	118 ± 16	114 ± 21
T <sub>3</sub> (nmol/L)	2.47 ± 0.44	2.73 ± 0.51 <sup>a</sup>	2.49 ± 0.68	2.57 ± 0.47	2.53 ± 0.62
T <sub>3</sub> /T <sub>4</sub> (×100)	1.81 ± 0.32	2.01 ± 0.39	1.85 ± 0.58	1.80 ± 0.33	1.84 ± 0.54
TBG (mg/L)	21.8 ± 3.4	24.1 ± 5.0	22.4 ± 5.9	22.9 ± 5.7	23.9 ± 5.6
TSH (mU/l)	2.30 ± 0.78	2.44 ± 1.15	2.00 ± 0.78	2.18 ± 0.70	2.23 ± 1.01
Cholesterol (nmol/L)	4.67 ± 0.68				4.64 ± 0.75
Triglyceride (nmol/L)	0.70 ± 0.27				0.80 ± 0.42

Data are the mean ± SD.

<sup>a</sup> P < 0.05.

centrations of T<sub>4</sub>, T<sub>4</sub>-binding globulin, and TSH did not change significantly during treatment. No correlation was found between the increase in the serum T<sub>3</sub> concentration and the change in bone maturation and height velocity of the patients during the first year of treatment.

#### Cardiovascular system

At the start of treatment, blood pressure was within normal limits in all patients, and no significant changes occurred during treatment (data not shown). Eight patients showed cardiac abnormalities; 5 had received surgery for an aortic coarctation and 1 for an aortic stenosis. In 1 patient, an abnormal pulmonary venous return and in another a mitral valve prolapse were found at echocardiography. In the vast majority of the patients (36 of 38), the pretreatment echocardiography showed that the posterior and septal wall thickness, internal diameter, and mass of left ventricle were below the 95th percentile confidence limit for body surface. After 1 yr of treatment, no significant increase in mean posterior or septal wall thickness was observed (Table 4). The mean internal diameter of the left ventricle at end diastole increased significantly after 1 yr of GH treatment (from 35.5 ± 5.0 to 38.9 ± 5.4 mm in the OD group and from 36.7 ± 2.7 to 40.0 ± 3.9 mm in the BID group). These changes in diameter were similar in the 2 groups (3.3 ± 3.9 vs. 3.3 ± 3.4 mm), but higher than expected for the increment in age and body surface (1.5 ± 0.5 mm; P < 0.05). However, these cavity measurements after 1 yr of treatment remained below the 95% percentile confidence limit for body surface in all patients. Also, the mean left ventricular mass increased significantly (P < 0.05) during therapy (from 62 ± 31 to 72 ± 39 g in the OD group and from 58 ± 17 to 70 ± 22 g in the BID group). These changes in left ventricle mass were, however,

**TABLE 4.** Echocardiographic parameters of left ventricular size at start and after 1 yr of GH treatment

	At start	At 1 yr
Left ventricular internal diameter (mm)		
OD (n = 19)	35.5 ± 5.0	38.9 ± 5.4 <sup>a</sup>
BID (n = 19)	36.7 ± 2.7	40.0 ± 3.9 <sup>a</sup>
Left ventricular posterior wall thickness (mm)		
OD (n = 19)	6.3 ± 1.6	6.1 ± 1.9
BID (n = 15)	5.8 ± 1.4	6.0 ± 1.8
Intraventricular septal wall thickness (mm)		
OD (n = 19)	6.4 ± 1.7	6.6 ± 1.7
BID (n = 19)	5.9 ± 1.1	5.9 ± 1.3
Left ventricular mass (g)		
OD (n = 19)	62 ± 31	72 ± 39 <sup>a</sup>
BID (n = 15)	58 ± 17	70 ± 23 <sup>a</sup>
Left ventricular mass (g/m <sup>2</sup> bs)		
OD (n = 19)	67 ± 16	70 ± 19
BID (n = 15)	65 ± 13	69 ± 17

Data are the mean ± SD.

<sup>a</sup> P < 0.05.

not significant if corrected for the change in body surface. The fractional shortening of the left ventricle, a parameter of left ventricular function, was normal in all patients and remained above the lower limit in all patients after 1 yr of treatment (data not shown). Patients with cardiac abnormalities showed changes in cardiac measurements similar to those in the other subjects during the GH therapy.

#### Clinical side-effects

GH treatment was well tolerated. Transient leg pains were mentioned by two girls, whereas in two others an increase

in skin nevi was reported. One girl complained of increased body hair, and the question of slower wound healing during GH therapy was addressed, but not proved, in one patient.

### Discussion

Our results showed that the administration of GH at a dose of 25 U/m<sup>2</sup>·week for 1 yr induced a significant growth acceleration in TS patients aged 4–16 yr. The growth data are comparable to those reported by others using a similar weekly dose of GH given as single daily injections (5, 7, 8).

In this study, we examined the possibility of further increasing the growth response by giving GH as twice daily injections. In GH-deficient children, Smith *et al.* (27) reported recently that a twice daily injection frequency resulted in a slight, but not significant, increase in growth rate during the first year of GH administration. In hypophysectomized rats, longitudinal bone growth was greater after GH administration as two or more frequent daily sc injections than after once daily injection (28). These observations and the physiological pattern of GH secretion as several daily pulses provided some arguments for dividing the daily dose of GH into two injections. We failed to show, however, that dividing equally the daily GH dose into morning and evening injections in TS patients resulted in a greater growth response than a single evening injection. In these patients treated with high doses, the tissue growth response to GH might be closely related to the peak GH concentrations achieved during therapy, which are lower in the twice daily regimen (29). In addition, two daily injections would result in greater suppression of endogenous GH secretion than a single daily injection. Compliance of the patients receiving twice daily injections was similar to that of the patients receiving once daily injections. Thus, compliance failure did not seem to have biased the data.

The ultimate effect of GH depends not only on the linear growth response, but also on skeletal maturation. In this study, mean BA progressed more rapidly than expected based on Ranke's standards for TS patients (17). However, comparison of our longitudinal data with cross-sectional standards could be misleading. Using dosages of GH similar to those used in our study, other investigators reported that bone age increased by a mean of 1 yr during the first year of therapy (5, 7). However, the previous data were usually obtained in older patients. As we found, in accordance with others (7, 8), that bone maturation progressed more rapidly in younger patients, age might explain the faster rate of bone maturation in this study. We did not observe any significant difference in bone maturation between TS girls treated using one or two daily injections.

So far, few data have been published on the side-effects of GH treatment in TS.

Although glucose tolerance was not affected by GH therapy, increased fasting or stimulated insulin concentrations were reported by some researchers after 1 yr of GH therapy, whereas no significant changes in insulin secretion were found by others, as in the present study (30, 31). Such a discrepancy could be related to the time period between the last GH injection and the assessment of insulin secretion. In the three of our patients who underwent OGTT less than 48

h after the last GH injection, increased insulin concentrations were seen. Therefore, the hyperinsulinemia observed by some researchers may result from an acute effect of GH lasting as long as treatment is given and disappearing soon after its cessation. We found it to be rather reassuring that five patients with impaired glucose tolerance showed a normal response to OGTT after 1 yr of GH therapy. However, we cannot exclude the possibility that long term GH therapy may cause significant glucose intolerance secondary to insulin resistance, although no such effect has been reported in TS patients treated for several years (32).

In agreement with other researchers, we found normal mean serum levels of cholesterol and triglycerides at baseline and during GH therapy (30, 33). A slight and transient, but not significant, increase in triglyceride concentrations was observed. This is in accordance with the findings reported by Wilson *et al.* (30). As increased triglyceride levels were reported in acromegalic patients, TS patients treated using high doses of GH deserve follow-up of blood lipid levels over the long term (34).

A transient alteration in serum T<sub>3</sub> concentrations was observed in our GH-treated TS girls; mean T<sub>3</sub> and T<sub>3</sub>/T<sub>4</sub> ratio were highest after 3 months of treatment. In normal men, a significant 23% increase in T<sub>3</sub> was observed during short term GH administration, whereas in TS girls, an increase in the T<sub>3</sub>/T<sub>4</sub> ratio after 6 months of GH administration has been reported (35, 36). The exact mechanism of these changes is unknown, and they seem to have no clinical implications. No correlation was found between these transient T<sub>3</sub> and T<sub>3</sub>/T<sub>4</sub> ratio changes and bone maturation or growth acceleration in our patients.

Several studies on cardiac size and function in acromegaly suggested that cardiac abnormalities may occur as a result of elevated GH concentrations; increased left ventricular wall thickness and increased wall mass were mainly reported (37, 38). In 16 children (13 with GH deficiency) treated with GH (0.17 U/kg) 3 times a week for several months or years, normal thickness of septal and posterior wall at echocardiography have been found retrospectively. In this study, higher doses of GH were used, and patients were followed prospectively. No abnormal increases in left ventricular wall thickness or mass could be demonstrated, even in patients with underlying cardiac abnormalities.

In conclusion, the daily administration of GH at a dosage of 25 U/m<sup>2</sup>·week stimulated linear growth significantly in TS girls aged 4–16 yr. The growth response was not different when dividing the daily dose into two injections. Although the increase in growth velocity was not related to age, bone age progression was faster in younger patients. Bone maturation was similar using one or two daily injections of GH. No significant changes in glucose and lipid metabolism were observed during or after 1 yr of GH administration. Although some thyroid function tests showed transient changes, they were found within normal limits. No abnormal increase in heart muscle thickness was observed during GH therapy.

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