CLINICAL STUDY

Adult height in girls with Turner syndrome treated from before 6 years of age with a fixed per kilogram GH dose

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Abstract

Objective: To evaluate adult height (AH) in 25 girls with Turner syndrome (TS) who were treated from before 6 years of age for 10.0 \pm 1.7 years with a fixed GH dose of 0.33 mg/kg per week.

Patients and design: After a 6-month pretreatment assessment all patients were measured 6-monthly under therapy to assess height SDS (H-SDS) and height velocity (HV) until AH achievement.

Results: Following initial acceleration, HV declined after the first 4 years of therapy. At the end of the sixth year of therapy, H-SDS gain was 1.9 \pm 1.1. Thereafter, H-SDS gain from baseline decreased, becoming 0.9 \pm 0.9 SDS at AH achievement. Bone maturation velocity did not significantly change throughout the prepubertal period. According to Lyon standards for TS, mean AH SDS was significantly higher than pretreatment H-SDS \((P<0.0001)\), with a mean H-SDS change of 0.9 \pm 0.9. However, the prevalence of patients with AH < -2 SDS (according to Sempe standards) was close to those recorded at the start of therapy (16/25 vs 18/25). No significant differences in terms of AH were found between patients with either X monosomy or X-chromosomal abnormalities and between girls with either spontaneous or induced puberty.

Conclusions: We infer that the therapeutic regimen adopted in this prospective study is sufficient to induce a significant growth acceleration during the first year, but the response waned after 6 years of treatment.

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Introduction

Short stature is the most constant finding in patients with Turner syndrome (TS). In past years it had been demonstrated that, in childhood, GH treatment with doses higher than those employed in GH deficiency can improve adult height (AH) in these patients (1, 2, 3). Therefore, it was widely accepted for many years that children with TS should be regularly treated with GH. More recently, a Cochrane analysis (2007) raised some concerns on the growth promotion effectiveness of this costly treatment and on the actual benefits that it allows in terms of patients’ quality of life (4). Following this meta-analysis (4), GH as a standard treatment in all children with TS has been recently questioned and debated (5, 6, 7). According to Rosenbloom & Fudge, ‘possible benefits from growth promotion must be weighed against the possibility that GH in pharmacological doses might adversely affect metabolism and mitogenesis over the long term’. These authors concluded that ‘initiation of GH therapy should be an individualized decision for each patient and her family’ (5). According to Ranke et al. (8), the new tools, such as prediction models, will eventually lead to a more meaningful use of GH in terms of efficacy, efficiency, and probably also safety, in the future (6, 7). According to Ross et al. (9), GH therapy in TS should be initiated as early as possible and then continued throughout the growth period, in order to optimize height gains in these patients.

In order to shed further light on this controversial matter, we have evaluated the AH outcome of 25 girls who had been treated for a mean period of 10 years, from before 6 years of age to AH achievement. The aim of this prospective study was to investigate whether prolonged GH therapy may enable TS patients to achieve an AH SDS close to target height (TH) SDS and higher than pretreatment H-SDS.

Subjects and methods

Study population

All 29 patients from our original study program (10) were included in the present study and fulfilled the...
following admission criteria: i) chronological age (CA) < 6 years at the commencement of treatment; ii) pretreatment height ≤−1 SDS and shorter than TH SDS; iii) pretreatment height velocity (HV) ≤−1 SDS; iv) absence of Y chromosome material; v) no other chronic medical conditions; and vi) no concomitant therapies that might interfere with growth.

Thereafter, four patients dropped out of the study and their AH was unavailable, due to moving to other regions. The main features of the remaining 25 patients at entry are reported in Table 1.

Pretreatment height was: i) ≤−3.0 SDS in 4/25 cases; ii) between −2.1 and −2.9 SDS in 14 girls; and iii) between −1.2 and −2.0 SDS in the remaining seven girls. Bone age (BA):CA ratio at entry was 0.9 ± 0.5.

**Study design**

Following a minimum of 6 months of baseline auxological observation, all patients underwent a prolonged (at least 6.5 years) hormonal treatment with biosynthetic human GH at a dose of 0.33 mg/kg per week, once daily. GH treatment duration in our series ranged from 6.5 to 12.3 years (mean 10.0 ± 1.7). From start of GH therapy to AH achievement, all patients were re-examined every 6 months, in order to monitor clinical and auxological progress. GH dose was adjusted every 6 months according to weight changes. BA was assessed at start of therapy and 6 years later.

No other hormonal therapy was given to any patient during the first 8.6 ± 0.9 years, while oral ethinylestradiol (at the initial dose of 2 μg/day) was begun at the age of 13 in the 20 girls who had exhibited no clinical signs of spontaneous puberty at that time. The five patients with spontaneous puberty underwent only GH treatment.

According to our study protocol, GH treatment was stopped in all girls when HV under therapy decreased to <2 cm/year (mean age at cessation 13.6 ± 0.8 years). Thereafter, all patients continued to be followed every 6 months until they achieved AH (at a mean age of 14.0 ± 1.0 years, range 12.1–15.3). AH was considered to have been reached when there was a linear HV of 4 mm/year or less measured over at least 6 months (11). The only girl who achieved AH at a relatively early age (12.1 years) had experienced spontaneous puberty.

The study protocol was approved by the Institutional Review Boards of each center and a written form was used to document the informed consents of patients’ parents at entry.

**Methods**

Height measurements of patients and their parents were performed using Harpenden stadiometers (Harpenden and Holtain Ltd., Crymmych, UK).

HV SDS, baseline height, TH, and AH SDS were calculated according to the growth standards of Sempé et al. (12). The effects of GH treatment on growth were evaluated as changes in H-SDS with respect to the Turner specific chart of Lyon et al. (13). The mean height changes that were recorded under therapy, and in particular the mean differences between AH SDS and starting H-SDS, were considered as direct measures of response to therapy.

For AH SDS, height gains were not calculated in relation to CA but using the reference data for 20 years of age, as in the paper by Sas et al. (14). Also for height measurements at GH treatment cessation, height SDS (H-SDS) gains were calculated in relation to the reference data for 20 years, considering that at therapy withdrawal, the majority of patients had already achieved AH and that the remaining 12 girls continued

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<th>Table 1 Main data at GH therapy onset and at adult height (AH) achievement in 25 girls with Turner syndrome.</th>
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<td><strong>Baseline</strong></td>
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<td>Chronological age (years)</td>
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<tr>
<td>Bone age (years)</td>
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<tr>
<td>Height velocity (SDS_Sempre)</td>
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<td>Height (SDS_Sempre)</td>
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<td>Target height (SDS_Sempre)</td>
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<td><strong>Adult</strong></td>
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<td>Chronological age (years)</td>
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<td>Time gap from therapy cessation to AH (months)</td>
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<td>AH (SDS_Sempre)</td>
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<td>AH (cm)</td>
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to grow at a \( \text{HV} \leq 4 \text{ mm/year} \) during the 6–12 months period that preceded AH achievement.

TH SDS was calculated by adding the parental H-SDSs (12) and dividing by 2.

In all the girls, BA was assessed by the same investigator using an X-ray image of the left hand and wirst, according to the method of Greulich & Pyle (15).

Pubertal development was estimated according to Tanner & Whitehouse (16).

**Statistical analysis**

Data are expressed as mean ± s.d., unless otherwise stated. Comparisons between groups were made by either unpaired or paired Student’s \( t \)-test or by Fisher’s exact test, as appropriate.

HV SDSs at multiple points were compared by the ANOVA for repeated measures. Post-hoc pairwise multiple comparisons were performed with the Bonferroni’s correction. Correlations were performed by Pearson’s test.

In all tests, \( P \) values < 0.05 (with Bonferroni’s correction where applicable) were considered to reflect the statistical significance. The Bonferroni’s corrected significance level for analysis of HV was \( P < 0.003 \).

**Results**

**HV and BA:CA ratio after GH therapy onset**

When compared with pretreatment growth rate, HV significantly increased during the first 4 years, achieving its zenith during the first year and subsequently declining (Fig. 1). After the fourth year of therapy, HV SDS progressively decreased, achieving its nadir during the sixth year of treatment (Fig. 1).

During the prepubertal study period, bone maturation velocity did not significantly change, as demonstrated by the substantially stable BA:CA ratio found

![Figure 1](image)  
**Figure 1** Mean (± s.d.) height velocity (HV) SDS at entry and during the first 6 years of GH treatment in 25 girls with Turner syndrome (\( P < 0.0001 \) with ANOVA for repeated measures; only significant differences in post-hoc analysis are shown). * \( P < 0.0001 \) vs entry.

**Adult height**

In 13 of 25 patients AH was already achieved at the time of GH treatment withdrawal, whereas in the remaining 12 patients it was achieved either 6 months (in six cases) or 12 months later (in six cases). During this time interval, HV of the 12 girls who had not already attained AH at the time of therapy cessation was \( \leq 4 \text{ mm/year} \).

In the whole series, the mean time interval between therapy cessation and AH attainment was \( 4.3 \pm 5.0 \) months (Table 1) and mean H-SDS\(_{\text{Lyon}}\) gain from therapy withdrawal to AH was \( 0.01 \pm 0.02 \) (Fig. 2).

Mean AH SDS\(_{\text{Sempe}}\) was not significantly higher than height recorded at the therapy start (\( P = 0.3 \)) and significantly less than TH (\( P < 0.0001 \)) (Table 1).

No significant differences in terms of AH SDS\(_{\text{Sempe}}\) were found between the five girls with spontaneous puberty (\( -1.9 \pm 0.9 \) SDS) and those with estrogen-induced puberty (\( -2.1 \pm 1.0 \) SDS), or between the 18 girls with X monosomy (\( -2.2 \pm 1.1 \) SDS) and those with other X-chromosomal abnormalities (\( -1.9 \pm 0.6 \) SDS). AH (cm) was not significantly associated with either treatment duration or TH.

Significant relationships were detected between AH (cm) and the heights measured at entry (\( r = 0.41, P = 0.009 \)), at the second (\( r = 0.46, P = 0.008 \)), the fourth (\( r = 0.54, P = 0.002 \)), and the sixth year of
treatment \((r=0.68, P=0.002)\), and at puberty onset \((r=0.52, P=0.008)\).

Mean AH SDS\(_{\text{Lyon}}\) was significantly higher than H-SDS at baseline \((P<0.0001)\), with a mean increase of \(0.9 \pm 0.9 \text{ SDS (Table 1)}\). Prevalence of girls with AH \(< -2.0 \text{ SDS}_{\text{Sempe}}\) was not significantly different from that recorded at therapy start: 16/25 vs 18/25 \((P=0.5)\).

**Discussion**

In this prospective study, we investigated the growth evolution under GH therapy and AH outcome of 25 girls with TS who began GH therapy before 6 years of age, and were treated for a mean period of 10 years, before achieving AH. This is an uncontrolled and non-randomized study covering a relatively small population. Nevertheless, it may be a useful contribution to the literature of GH therapy in TS, firstly in that it documents the long-term response to a treatment begun at relatively young ages and, secondly, it allows assessment of the long-term effects of a fixed per kilogram dose in this condition.

Age at initiation and duration of GH therapy is known to be an important factor in determining GH effectiveness and, therefore, such treatment in TS should be started as soon as growth failure is observed (17). Early onset of GH therapy not only allows longer duration of treatment, but utilizes a window of higher responsiveness in these girls (18). However, so far no data on AH in these early treated cohorts have been published (7), apart from a paper by Van Pareren et al. (2), whose patients were between 2 and 11 years of age at start of therapy.

The results of this study confirm that most girls with TS can exhibit an important height improvement during the first years of GH therapy, and also recently reported by other authors in early treated patients (17, 18, 19). By contrast, long-term auxological results of treatment may not be so positive, as is suggested by our findings. In fact, long-term results of GH therapy in this series might be regarded as relatively disappointing, considering that: i) treatment was initiated at a relatively young age and prolonged for a mean period of 10 years; ii) an important H-SDS gain had already occurred during the first 6 years of treatment; iii) the mean H-SDS change from therapy onset to AH achievement was 0.9 SDS\(_{\text{Lyon}}\) (0.3 SDS\(_{\text{Sempe}}\)); and iv) mean AH SDS\(_{\text{Sempe}}\) was significantly less than TH.

The mean AH of our patients (149.1 cm) was close to that (147.9 cm) recently reported by Ross et al. (20) in one of the most relevant studies of GH treatment in TS. These authors conducted a double-blind placebo-controlled trial that adopted a fixed per kilogram GH dose. Mean AH (cm) was also similar to that recorded in other studies, where patients commenced treatment at a more advanced age (21, 22) and the per kilogram GH doses throughout study periods were not fixed. In other TS studies, the prevalence of treated patients with AH < -2 SDS ranged from 32% (23) to 64% (24), as in this study.

Growth responsiveness during the first year of GH therapy has been reported to be one of the major determinants of height improvement in TS patients treated with GH (22, 25). However, the overall GH dose seems to be another important factor influencing the magnitude of height gain under therapy, with the best long-term results obtained in the patient groups treated with the highest GH doses (2, 21, 25, 26).

Although a physiological decline over time in growth response to treatment has been reported in TS (2, 18, 24, 26), the progressive increments of GH doses, aiming to counteract the gradual waning effect of this therapy, were proposed (2). Nevertheless, the waning effect observed with conventional GH doses has been reported to be only partially prevented by incrementing GH doses (24), and incremental dosing after the first year may not completely reverse it (18).

To sum up, on the basis of our results, we can infer that the therapeutic regimen adopted in this study may be sufficient to induce a significant growth acceleration during the first year, but the initial response may wane after 6 years of the treatment.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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