CLINICAL STUDY

Adult height after GH therapy in 188 Ullrich–Turner syndrome patients: results of the German IGLU Follow-up Study 2001

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Abstract

Objectives: We aimed to evaluate the factors influencing true adult height (HT) after long-term (from 1987 to 2000) GH treatment in Ullrich–Turner syndrome (UTS) based on modalities conceived in the 1980s.

Design: Out of 347 near-adult (>16 years) patients from 96 German centres, whose longitudinal growth was documented within KIGS (Pharmacia International Growth Database), 188 (45, X = 59%; bone age >15 years) were available for further anthropometric measurements.

Results: At a median GH dose of 0.88 (10th/90th percentiles: 0.47/1.06) IU/kg per week, a gain of 6.0 (–1.3/+13) cm above the projected adult height was recorded. Variables were recorded at GH start, after 1 year GH, puberty onset, and last visit on GH therapy. At these visits, the median ages were 11.7, 12.7, 14.2, 16.6 and 18.7 years; and median heights, 0.4, 1.1, 1.7, 1.7 and 1.3 SDS (UTS) respectively. Height gain (Δ HT) after GH discontinuation was 1.5 cm. Total Δ HT correlated ($P < 0.001$) negatively with bone age and HT SDS at GH start, but positively with Δ HT after the first year, Δ HT at puberty onset, and GH duration. Final HT correlated ($P < 0.001$) positively with HT at GH start, first-year Δ HT, and HT at puberty onset. Body mass index increased slightly ($P < 0.05$), with values at start and adult follow-up correlating highly ($R = 0.70$, $P < 0.001$). No major side effects of GH occurred.

Conclusions: GH dosages conceived in the 1980s are safe but too low for most UTS patients. HT gain and height are determined by age and HT at GH start. Height gain during the first year on GH is indicative of overall height gain. After spontaneous or induced puberty, little gain in height occurs.

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Introduction

The availability of recombinant human growth hormone (rhGH) since the 1980s has led to the exploration of its growth-promoting effects in various growth disorders. In a study of girls with Ullrich–Turner syndrome (UTS), Rosenfeld *et al.* were the first to prove that adult height could be improved by GH (1). In the 1980s, several similar studies were conceived, but their published results left doubts about the extent of height gain that could be achieved through GH therapy alone or in combination with oxandrolone (see Donaldson for a review (2)). In most of these studies, GH therapy was initiated at a relatively late age, with the GH dose being about 1.5 times the replacement doses

used in treating GH deficiency. Recent studies, in which much higher doses were applied in younger patients, have confirmed that normalisation of height is a goal that can be achieved in UTS (3, 4). Multivariate analyses of the factors influencing height outcome have also shown that the most important factors are GH dose and age at the start of GH treatment (5). There is also accumulating evidence showing that oestrogen replacement for the induction of puberty limits further gains in height (6–8). However, even though dosage appears to be one of the essential determinants of the growth effect, most studies have shown that the short- and long-term response to GH is rather variable. Our aim in conducting this follow-up study was to evaluate the long-term effects of GH in a large cohort

of adult UTS patients. The source of data for our analysis derived from the documentation of patients who were primarily observed in a previous study on the efficacy and safety of rhGH (Genotropin) which began in 1986. Although a number of investigations were carried out in the follow-up study, our focus here will be on height outcome.

Patients and methods

Until January 2000, the Internationale Genotropin Langzeit-Untersuchung (IGLU) database, which is the German segment of Pharmacia International Growth Database (KIGS), documented UTS patients from 96 German centres, 347 of whom had reached near-adult height (age > 16 years) at the time. The patients were initially included in a GH product trial (Genotropin) focusing on safety and efficacy, which began in 1986 in Germany. After GH was approved for the treatment of short stature in UTS, the data of these patients continued to be documented within the framework of KIGS, which was structured as a pharmaco-epidemiological survey. The last visit documented in IGLU marks the end of GH treatment and is referred to as the 'last IGLU visit'. In order to evaluate the results of treatment in terms of true adult height (bone age > 15 years), the participating centres agreed on a standardised follow-up visit for patients belonging to this group. The follow-up was conducted according to a protocol approved by the Ethics Committee of the participating institutions, and written, informed consent was obtained at the time of the follow-up visit. A total of 188 patients returned for examination, their data providing the basis for our present analysis. Karyotype details were supplied by the referring physicians.

The anthropometric data were analysed according to previously described criteria (9). Reference values for height and midparent height (MPH) were taken according to the standards of Tanner *et al.* (10, 11). Weight and body mass index (BMI) were calculated on the basis of the British references of Freeman *et al.* (12). Birth weight and length were compared to the references of Niklasson *et al.* (13). We applied the height references for UTS of Ranke *et al.* (14) and weight and BMI references of Schweizer *et al.* (6). Standard deviation scores (SDS) for age were calculated.

On the model derived by Ranke *et al.* (15) we carried out the prediction of height velocity (cm/year) and calculation of studentised residuals (SR = (observed height velocity (cm/year) minus predicted height velocity (cm/year)) / residual of predicted height velocity (cm/year)) during the first year of treatment. Projected adult height (PAH) was calculated according to UTS standards of height (14). The onset of puberty was assumed either when breast stage II according to Tanner was observed or therapy with oestrogens was initiated. Bone age was rated according to Greulich &

Pyle (16). The dose of GH was expressed in terms of IU/kg body weight (BW) per week (3 IU = 1 mg). All patients received daily injections of GH. At the time of follow-up, all patients were receiving oestrogens or had spontaneously entered puberty, while in 15 patients this was not the case at the time-point of the last IGLU visit. Medians, 10th and 90th percentiles, Spearman correlation coefficients and Kruskal-Wallis tests were used to obtain *P* values. A value of *P* < 0.01 was considered significant.

Results

The distribution of karyotypes within the group of patients investigated (*n* = 188) is listed in Table 1. We observed the 45,X karyotype in 58% of patients, whereas in ten patients with complete female phenotype the karyotype 45,X/46,XY was determined. Table 2 offers a selection of characteristics describing the group as a whole at various time-points, i.e. at the start of GH treatment, onset of spontaneous or induced puberty, the last IGLU visit and at the time of follow-up for this study. Information (medians) about the 159 patients of the original cohort (*n* = 347) who did not respond to the follow-up request is given for the relevant time-points in Table 2. In addition, the karyotype 45,X was observed in 58% of this subset, and there was no statistically significant difference between any parameter (*P* > 0.1). As in other UTS cohorts, size at birth was lower by about 1 SDS, but parental height was normal. Treatment with GH started at a median age of 11+ years. Height at start was insignificantly higher than that of the German UTS reference population (14). Consequently, the PAH was slightly higher than the average adult height for German UTS references (148.8 vs 146.3 cm). The starting dosage of GH averaged 0.9 IU/kg BW per week and remained nearly constant (with the decrease being very insignificant) over the years. Height and weight for all patients at start and in comparison to UTS references

Table 1 UTS karyotypes represented in our study (*n* = 188).

Karyotype	<i>n</i>	%
45,X	110	58.5
45,X/46,XX	19	10.1
45,X/47,XXX	5	2.7
45,X/46,XX/47,XXX	2	1.1
45,X/46,X, i (Xq)	16	8.5
45,X/46,X, r (X)	5	2.7
46,X, i (Xq)	9	4.8
46,X, del (Xq)	1	0.5
46,X, del (Xp)	1	0.5
45,X/46,X,del (Xq)	3	1.6
45,X/46,X,del (Xp)	1	0.5
45,X/46,XY	10	5.3
Others	6	3.2

Table 2 Characteristics of UTS patients ($n = 188$) before, during and after GH therapy.

Variables	Follow-up group (<i>n</i> = 188)			Group not seen for follow-up (<i>n</i> = 159)		
	Median	Percentiles		Median	Percentiles	
		10th	90th		10th	90th
Background						
Birth weight (SDS)	− 1.1	− 2.9	− 0.1	− 1.3	− 2.8	0.3
Birth length (SDS)	− 0.5	− 3.0	0.9	− 0.5	− 1.9	1.2
MPH (SDS)	0.2	− 1.3	1.7	0.5	− 0.9	1.8
At GH start						
Age (years)	11.7	8.9	14.8	12.4	8.1	15.2
Bone age (years)	10.0	7.3	12.5	10.5	7.0	13.0
Height (Tanner) (SDS)	− 3.7	− 4.9	− 2.4	− 3.7	− 5.6	− 2.8
Height (SDS)	0.4	− 1.1	1.8	0.3	− 1.0	1.6
PAH (cm)	148.8	139.9	157.2	148.4	139.9	155.9
BMI (SDS)	0.4	− 1.3	1.8	0.4	− 0.9	1.7
GH dose (IU/kg per week)	0.88	0.47	1.06	0.84	0.47	1.03
After 1 year on GH						
Height (Ranke) (SDS)	1.1	− 0.3	2.5	1.0	− 0.5	2.2
ΔHT (Ranke) (SDS)	0.7	0.3	1.2	0.6	0.2	0.9
At start of puberty						
		(<i>n</i> = 173)			(<i>n</i> = 112)	
Age (years)	14.2	12.4	17.0	14.3	12.6	16.5
Bone age (years)	12.0	10.5	13.5	12.5	11.0	13.5
Height (Ranke) (SDS)	1.7	0.0	2.9	1.3	0.0	3.0
ΔHT (Ranke) (SDS)	1.1	0.4	2.2	0.9	0.1	2.1
Years on GH (years)	2.4	0.8	5.0	2.1	0.5	5.3
At last IGLU visit						
Age (years)	16.6	14.7	19.3	16.5	15.3	19.2
Height (cm)	150.7	142.4	158.0	150.3	143.5	157.9
Height (Ranke) (SDS)	1.7	0.0	3.0	1.7	0.1	2.9
BMI (SDS)	0.7	− 1.0	2.2	0.7	− 0.5	2.3
ΔHT (Ranke) (SDS)	1.3	0.3	2.3	1.2	0.3	2.2
Years on GH (years)	4.5	2.2	7.3	4.4	1.9	8.0
At follow-up						
Age (years)	18.7	16.0	23.6			
Height (cm)	152.2	144.0	159.8			
Height (Ranke) (SDS)	1.3	− 1.1	2.6			
BMI (SDS)	0.7	− 0.9	2.5			
ΔHT (Ranke) (SDS)	1.0	− 0.2	2.1			
Gain over PAH (cm)	6.0	− 1.3	13.0			

are illustrated in Fig. 1a and b. The height increment (Δ HT SDS for UTS) during the first year on GH averaged 0.7 SDS with 90% exceeding 0.3 SDS. Puberty was observed after 2.4 years (median) on GH, at an age of 14.2 years and a bone age of 12.0 years. By that time, height SDS exceeded the UTS references by 1.7 SDS and a total height gain of 1.1 SDS was recorded. In comparison to the height values for UTS references (SDS) there was, on average, no significant further height gain after puberty began. During the 2 years between the last IGLU visit and follow-up visit, we observed an average height gain of 1.5 cm in the total group ($n = 188$), whereas among the 39 patients with spontaneous puberty it averaged 1.1 cm; in 134 patients with induced puberty after the last IGLU visit it averaged 1.4 cm, and in the group of 15 patients who did not enter puberty before the last IGLU visit it averaged 3 cm.

Table 3 shows the median values for characteristic parameters at the start of GH therapy, at the onset of puberty, the last IGLU visit and at follow-up, for the sub-groups of patients, i.e. those with spontaneous puberty ($n = 39$), induced puberty ($n = 134$) and no evidence of puberty during the course of the IGLU study ($n = 15$). There were no statistical differences between the auxological characteristics at the start of treatment and the outcome of GH therapy. In 35 patients, oxandrolone (0.05 mg/kg per day) was introduced during GH treatment, however, the characteristics of these patients did not differ from the other groups (data not shown).

In order to evaluate the height outcome in terms of both gain in height (Δ HT SDS UTS) and actual height achieved (centimetres), the variables were correlated with various parameters during the course of treatment. The results are listed in Table 4 and illustrated in Fig. 2.

Figure 1 Height (a) and weight (b) of UTS patients ($n = 188$) at start of GH treatment in comparison to German UTS references. Broken lines indicate ± 2 S.D. ranges; shaded areas indicate height range for normal girls.

Our results showed that the outcome variables of height correlated with variables before as well as during the first year of treatment. The gain in height (S.D.) and absolute height (cm), however, did not correlate with the same predictors. The overall gain in height (Δ HT SDS) was found to correlate with (a) auxological characteristics at the start of treatment (age, bone age (the lower, the better); height; BMI; HT minus MPH (= height distance to target height) (the smaller, the better)); (b) modalities of treatment (starting dose, mean dose, total dose (the higher, the better); years on GH (the longer, the better)); (c) auxological characteristics at onset of puberty (bone age (the lower, the better); total pre-pubertal growth (the more, the better)); and (d) first-year growth response (height velocity, studentised residual (the higher, the better)).

Adult height in absolute terms (centimetres) correlated with (a) auxological characteristics at start of treatment (height (the taller, the better)); (b) modalities of treatment (total dose (the higher, the better), years on GH (the longer, the better)); (c) auxological characteristics at onset of puberty (height (the higher, the better); total pre-pubertal growth (the more, the better)); and (d) first-year growth response (height

velocity, studentised residual (the higher, the better)). Height observed at follow-up and height predicted at start of therapy by means of a previously published descriptive model (17) correlated highly ($R = 0.72$, $P < 0.001$).

None of the patients suffered from serious side-effects of GH therapy during follow-up. In particular, we did not observe the development of diabetes mellitus in any of the patients. In a sub-population of 90 patients, we had information on fasting blood glucose (BG), glycosylated haemoglobin (HbA1c), and total cholesterol (TC), this data being provided by the participating institutions. BG levels were 85.0 ± 9.5 mg/dl (mean $\pm$ S.D.), and, in one case, was 111 mg/dl. HbA1c levels were $5.1 \pm 0.6\%$ (mean $\pm$ S.D.), with four patients exceeding 6.0% (one patient had 6.7%). The TC levels were 174 ± 27 mg/dl (mean $\pm$ S.D.).

The BMI SDS were found to have increased between the start of GH treatment (median: 0.4 SDS) and follow-up (median: 0.7 SDS) when compared with normal references (see Table 2). The values at final height correlated positively ($R = 0.70$, $P < 0.001$) with the level at the start of therapy. In comparison with Turner-specific references (6), however, no increment in BMI was observed over time in the treated group (Fig. 3).

Table 3 Differentiation of UTS patients according to pubertal type (in median values).

Variables	Total	Groups		
		Spontaneous puberty	Induced puberty	No puberty
Number	188	39	134	15
At GH start				
Age (years)	11.7	11.5	11.8	11.3
Bone age (years)	10.0	10.3	10.0	9.0
Height (UTS) (SDS)	0.4	0.6	0.4	0.0
PAH (cm)	148.8	149.6	148.9	148.3
GH dose (IU/kg per week)	0.88	1.00	0.81	0.96
At start of puberty				
Age (years)	14.2	14.2	14.3	—
Bone age (years)	12.0	12.6	12.0	—
Height (UTS) (SDS)	1.7	1.8	1.5	—
Δ HT (Ranke) (SDS)	1.1	1.2	1.1	—
Years on GH (years)	2.4	2.6	2.4	—
At last IGLU visit				
Age (years)	16.6	16.9	16.5	15.6
Height (cm)	150.7	151.3	150.9	147.8
Height (UTS) (SDS)	1.7	1.7	1.8	1.6
Years on GH (years)	4.5	5.1	4.5	3.4
At follow-up				
Age (years)	18.7	19.5	18.5	18.8
Height (cm)	152.2	152.4	152.3	150.8
Height (Ranke) (SDS)	1.3	1.3	1.3	1.5
Δ HT (Ranke) (SDS)	1.0	0.8	1.0	1.1
Gain over PAH (cm)	6.0	5.0	6.1	7.0

Table 4 Simple linear correlation of height outcome and patient characteristics during observation.

Variable	Δ HT SDS (UTS)			Adult HT (cm)		
	<i>n</i>	<i>R</i>	<i>P</i>	<i>n</i>	<i>R</i>	<i>P</i>
At GH start						
Age (years)	188	−0.274	<0.001	188	−0.048	NS
Bone age (years)	162	−0.530	<0.001	162	−0.014	NS
Height (UTS) (SDS)	188	−0.56	<0.001	188	0.627	<0.001
HT MPH (SDS)	178	−0.284	<0.001	178	−0.037	NS
BMI (SDS)	188	−0.268	<0.001	188	0.053	NS
GH dose (IU/kg per week)	188	0.217	<0.003	188	0.015	NS
First year on GH						
Δ HT (SDS)	188	0.456	<0.001	188	0.243	0.001
Studentised residual	102	0.375	<0.001	102	0.232	0.019
At start of puberty						
Age (years)	133	0.103	NS	133	0.096	NS
Bone age (years)	125	−0.242	0.007	125	0.105	NS
Height (UTS) (SDS)	133	−0.082	NS	133	0.745	<0.001
HT MPH (SDS)	125	0.004	NS	125	0.136	NS
Pre-pubertal						
Δ HT (SDS)	133	0.682	<0.001	133	0.279	0.001
Mean GH (IU/kg per week)	125	0.035	NS	133	−0.111	NS
At end of follow-up						
Age (years)	188	−0.191	0.008	188	0.130	NS
Duration of GH therapy (years)	188	0.465	<0.001	188	0.264	0.035
Total GH dose (IU/kg per week)	188	0.380	<0.001	188	0.264	<0.001
Mean GH dose (IU/kg per week)	188	0.183	0.012	188	−0.076	NS

Figure 2 Factors influencing total height gain, showing correlation between total Δ HT (SDS) and (a) bone age at GH start, (b) height at start (SDS Turner references), and (c) total dose of GH (IU).

Discussion

It has become general practice in many countries to treat UTS patients with GH in order to improve short

stature. There are, however, few reports on the adult height outcome of long-term GH treatment (2, 18–24). It must be remembered that the final height gained reflects treatment concepts that were developed

Figure 3 Factors influencing total height gain, showing correlation between total Δ HT (SDS) and (a) first-year Δ HT (SDS Turner references), and (b) first-year studentised residuals.

almost two decades ago. Since that time, several determining factors relating to the short-term response to GH have been identified (25), the most significant among them being the age at GH start (the younger, the better), and the GH dose (the higher, the better). In contrast, relatively little knowledge is available about the factors determining the development of adult height (9). An analysis of patients treated with intermediary GH doses (e.g. <1.0 IU/kg per week) seems particularly important, since it appears that not all UTS patients necessarily need to be treated with high GH doses; conversely, long-term GH treatment may not be suitable at all in certain cases.

The present study, drawing on data from a national cohort of patients treated with one brand of GH, represents the first large study where a follow-up of true adult height was done after GH treatment ended. The genetic composition of the cohort investigated concurs with other large series (6). The advanced age at start of GH treatment partly reflects the age at the time UTS was diagnosed but also involves a certain bias resulting from the fact that final height is achieved within a shorter period of treatment. The height at start of GH is only slightly higher than that of historical German references (14). The GH dose was within a rather narrow range of 0.45–1.1 IU/kg per week, which is similar to other studies conceived in the 1980s (2).

The characteristics at start of GH, after 1 year on GH, at puberty onset and at the time of the last regular KIGS visit, were not different in the 159 patients who did not return for the follow-up visit, which indicates that there is no selection bias for the 188 patients analysed. The availability of data, however, made it feasible to prove true adult height only in the latter patients.

It is interesting to note that only 15 of 188 patients were not pubertal and had not received oestrogen replacement even at the time of the last IGLU visit. The oestrogen replacement was, on the average, delayed until the patient reached approximately 14 years of age, i.e. corresponding to a bone age of 12 years. This may reflect the prevailing therapeutical approach of physicians in view of the doubtful magnitude of the GH effect on growth.

The late introduction of oestrogens appears to be a decisive factor influencing height outcome in patients treated with similar doses of GH, as other investigations (6, 26) have shown. Since the spread of age at pubertal onset was, however, relatively narrow, our data do not allow a complex multiple regression analysis relating puberty with adult height in UTS.

It is remarkable that we observed only an average gain of 1.5 cm between the last IGLU visit and the follow-up after 2 years. These findings are valuable in terms of counselling as they allow realistic expectations relating to the growth process after GH treatment ends. The present study provides further, strong support for the thesis that GH treatment offers UTS patients the means to achieve a substantial gain in height. Our

results also confirm, however, that the total gain in height over projected height proved to be variable, a fact that was also true for the height outcome in terms of absolute height. The median gain in height above PAH averaged 6.0 cm after 4.5 years on GH, which correlates with the results found in similar cohorts that received comparable GH doses (2). The major correlates of height gain were bone age (negative) and height SDS (UTS) (negative) at start of GH, the first-year growth during GH therapy (positive), the overall pre-pubertal height gain (Δ HT SDS) (positive), GH dosing (positive), and the duration of treatment (positive).

It can be assumed that duration of treatment is a function of age at GH start as well as the time at which the closure of epiphyses (puberty) began. It is realistic to expect that the pre-pubertal height gain positively correlates with overall height gain, since the onset of puberty occurred towards the end of growth, and was later in the UTS patients. It is remarkable to note, however, that first-year growth and responsiveness to treatment (as expressed in terms of the studentised residual) show a high correlation with overall height gain. This appears to indicate that the response to GH is a quality that is specific to each individual patient. In practical terms, this would mean that a girl whose first-year height gain is below 0.4 SDS (UTS) and with a studentised residual below -1.0 is very unlikely to have a total gain in height of more than 6 cm ($= 1.0$ SDS UTS) on a GH dose of 0.9 IU/kg per week. While the gain in height is greater if a UTS patient is relatively short, the absolute height outcome is better in cases of UTS girls who are already relatively tall. This means that a tall UTS girl is not likely to gain much height through low-dose GH treatment, but will likely reach the PAH with high probability. If the method of height projection were also a truly precise measure in patients with extremes of height for UTS (<-1.0 SDS; $>+1.0$ SDS), it would follow that children whose PAH is within the normal range need not be treated with GH. It is remarkable that the analysis of data concerning low-dose GH ranges shows that dosage is important for the short-term as well as long-term gain in height, but to a lesser degree for the achievement of absolute height. Following this reasoning, it can be presumed that in relatively tall children, in whom the outcome in height tends to be favourable, only higher doses than applied here are probably necessary in order to be effective. These findings indicate that an increase in the GH dose, in order to induce a response (cm/year; Δ HT SDS), can probably be avoided, thus reducing the high costs of GH therapy in some UTS patients. Studies in which there is no control of GH dosage may also lead to false conclusions, because observations of the response – rather than responsiveness to GH – may lead to higher GH doses among poor responders. Thus, in terms of the final height outcome, our study shows

that the responsiveness during the first year on GH is important. Since the aim of treating short stature in UTS is to achieve the normalisation of height and, at the same time, induce the normal timing and progression of puberty, the therapy needs to focus on the first pre-pubertal years.

Future studies should aim to compare the results of continuous GH treatment with those of interrupted treatment (such as the type suggested for the observation of small-for-gestational-age patients (27)), in which various dose levels are applied, and in which the early response as well as responsiveness to GH are taken into consideration.

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