Clinical Endocrinology (2011) **74**, 473–480 doi: 10.1111/j.1365-2265.2011.03937.x

ORIGINAL ARTICLE

Growth hormone treatment for Turner syndrome in Australia reveals that younger age and increased dose interact to improve response

Ian P. Hughes*, Catherine S. Choong†, Mark Harris‡, Geoffrey R. Ambler§, Wayne S. Cutfield¶, Paul L. Hofman¶, Chris T. Cowell§, George Werther**, Andrew Cotterill‡ and Peter S.W. Davies* on behalf of the Australasian Paediatric Endocrine Group (APEG)

**The Children's Nutrition Research Centre, Discipline of Paediatrics and Child Health, School of Medicine, The University of Queensland, Brisbane, Qld, †Department of Endocrinology and Diabetes, Princess Margaret Hospital for Children, Subiaco, WA, ‡Department of Paediatric Endocrinology, Mater Children's Hospital South Brisbane, Qld, §Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Westmead, NSW, Australia, ¶Liggins Institute, University of Auckland, Auckland, New Zealand, **Department of Endocrinology and Diabetes and Centre for Hormone Research, Royal Children's Hospital, Parkville, Vic., Australia*

Summary

Objective To investigate response to growth hormone (GH) in the first, second and third years of treatment in the total clinical cohort of Turner syndrome (TS) patients in Australia.

Context Short stature is the most common clinical manifestation of TS. GH treatment improves growth.

Design Response was measured for each year of treatment. Stepwise multiple regression analyses were used to identify factors that significantly influenced response.

Patients Prepubertal TS patients who completed 1 year (n = 176), 2 year (n = 148), or 3 year (n = 117) of treatment and were currently receiving GH.

Measurements Change in TS specific Height Standard Deviation Score (ΔTSZ) was the main response variable used. Major influencing variables considered included dose, starting age and height, BMI, bone age delay, karyotype, parental height, and interactions between dose and starting age or height.

Results Response was greatest in first year and declined thereafter (median ΔTSZ: 1st year = +0·705, 2nd year = +0·439, 3rd year = +0·377) despite the median dose increasing [1st year = 5·5 mg/m^2/week (0·23 mg/kg/week), 2nd year = 6·4(0·24), 3rd year = 7·2(0·26)]. An Age*Dose interaction was identified influencing first, second year, and total ΔTSZ. The ΔTSZ over 3 years was significantly influenced by first-year dose. Dose increments only attenuated the general decline in response. An acceptable first-year response (ΔTSZ > 1·01) was achieved by only 17·6% of patients.

Conclusions Growth response is greatest and most influenced by dose in the first year. Dose in first year is a major factor contributing to total response. A starting Age*Dose interaction effect was observed such that young girls on a high dose respond disproportionately better. Optimal GH treatment of short stature in TS thus requires early initiation with the highest safe dose in the first year.

(Received 30 September 2010; returned for revision 6 November 2010; finally revised 18 November 2010; accepted 19 November 2010)

Correspondence: Ian Hughes, The Children's Nutrition Research Centre, Discipline of Paediatrics and Child Health, School of Medicine, The University of Queensland, Level 3 Foundation Building, Royal Children's Hospital, Herston, Qld 4029, Australia. Tel.: 61 7 3365 5576; Fax: 61 7 3346 4684; E-mail: i.hughes@uq.edu.au

Introduction

In this report, we examine treatment in a nationwide growth hormone (GH) treatment program for Turner syndrome (TS) by focussing on the first-, second-, and third-year response of all prepubertal girls receiving GH for TS in Australia in 2007. It follows on from and makes contrasting reference to two earlier Australian studies[1,2] to report on GH treatment of TS.

TS results from the total or partial loss of one X chromosome in females. This loss may affect all cells, or the individual may be a mosaic of affected and normal cell lines. It is the most common chromosomal disorder affecting females and is reported to affect 1 in 1800–5000 live-born girls, although at conception the rate is as high as 3% with 99% of these spontaneously aborting[3–5] TS consists of a wide range of characteristic phenotypic features of which short stature is one of the most frequent. Without intervention, TS women are approximately 20 cm shorter than unaffected peers.[4–6] The short stature phenotype is, at least partly, attributable to haploinsufficiency of the pseudoautosomal SHOX gene (short stature homeobox-containing gene; Xp22·33 and Yp11·3)[7] Although there is no abnormality in the GH/insulin-like growth factor-1 axis, GH

treatment at supra-physiological doses improves height gain in the short term and final adult height outcome.[4–6]

The Australian program is possibly unique in at least two aspects as dosing is based on body surface area (BSA) and that the mean dose is lower than that used in other countries.[1,2,4,8–14] A critical appraisal of the efficacy of GH treatment in this cohort, particularly in reference to these points of difference, may be useful for paediatric endocrinologists to identify treatment strategies for improving growth outcomes for TS in other countries as well as Australia.

Materials and methods

Subjects

Treatment data and basic demographic and clinical information on all children receiving GH as part of the Australian Government's Pharmaceutical Benefit Scheme (PBS) are recorded in a national database (OZGROW). In all cases, informed consent is obtained from the patient's parent/guardian for this data to be used for research into, and evaluation of, GH use under the PBS program. Information is de-identified to maintain patient confidentiality. In this study, TS patients were selected who were currently recorded as receiving GH (as of third December 2007), were prepubertal, had made at least one visit to a growth clinic in 2007, had received GH for more than 39 weeks (first-year response analysis), 91 weeks (second-year response analysis), or 143 weeks (third-year response analysis), and for which GH dose rates were available at each visit to a growth clinic. A total of 176 girls fulfilled the above criteria for the first year 148 for the second year, and 117 in the third year.

Requirements for subsidized GH treatment

Girls with TS are eligible to receive GH treatment if their height is at or below the 95th centile on a Turner-specific chart[15] as detailed in 'Guidelines for the Availability of Human Growth Hormone (hGH) as a Pharmaceutical Benefit'.[16]

In Australia, the Commonwealth Department of Health and Ageing (DoHA) allows a dose range from 4·5 to 9·5 mg/m^2/week for Turner syndrome. In this report, dose has been presented in both mg/m^2/week and mg/kg/week forms for the purpose of comparison. Median doses reported in the literature range from 0·23 to 0·36 mg/kg/week.[4,8–14] The median first-year dose reported in our cohort was 5·5 mg/m^2/week, which is approximately equivalent to 0·23 mg/kg/week.

Height and weight measurements

Height, weight, and age were recorded at each visit to a growth centre. Height and weight were measured by experienced clinical nurses or paediatricians using standard auxological methods. Height measurements were converted to SDS, or Z values, according to age at measurement using the Turner syndrome-specific formulas of Haeusler *et al.*[17] with reference also to the Turner syndrome standards of Lyon *et al.*[15] As some previous studies have used height SDS based on the general population of girls, for the purpose of comparison, we also calculated height SDS according to the United States Growth Charts of the Centers for Disease Control and Prevention (CDC).[18] Growth velocity (GV) was also calculated and converted to TS-specific Z values.[17] BMI was converted to a Z score based on CDC standard data.[18]

Height (Ht) and weight (Wt) measurements were used to estimate BSA using Mosteller's[19] formula $\mathrm{BSA}(m^2) = \sqrt{\frac{\mathrm{Ht(cm)} \times \mathrm{Wt(kg)}}{3600}}$. With a knowledge of BSA, dose (mg/m^2/week), and weight the dose in terms of mg/kg/week could be calculated. In a majority of cases, heights of both parents were available by either measurement or self-report. Parental heights were converted to height SDS using the LMS procedure and the CDC Growth Charts.[18] The mean parental height SDS could then be calculated: $\mathrm{Ht(SDS)}_{\mathrm{Mid-parent}} = \frac{\mathrm{Ht(SDS)}_{\mathrm{Father}} + \mathrm{Ht(SDS)}_{\mathrm{Mother}}}{2}$. Similarly, most individuals had bone ages (BA) available, which allowed a BA to chronological age (CA) difference to be calculated.

Analyses

Response to GH treatment in first, second, and third years was measured as change in Turner-specific height SDS (ΔTSZ) or as the Turner-specific SDS of GV (GVZ). First-year response was measured as ΔTSZ1 or GVZ1 over the first 52 weeks of treatment. In practice, the visit closest to being 52 weeks since the commencement of GH was identified and the response normalized to 52 weeks. Similarly, second- (ΔTSZ2, GVZ2) and third-year (ΔTSZ3 or GVZ3) response was measured over subsequent blocks of normalized 52 weeks of treatment. A number of factors were investigated with regard to their potential influence on ΔTSZ or GVZ response. These were mean dose per week during the first, second or third year of treatment (mg/m^2/week or mg/m^2/week), mean parental height SDS, age at commencement of GH treatment, height SDS (TSZ) at start of that year of treatment, body mass index Z-score at start of that year of treatment (BMI-Z), difference between bone and chronological age (BA-CA), and karyotype (monosomy, mosaic, isochromosome/deletion). In addition, for second and third years, the ΔTSZ or GVZ recorded in previous years were used as factors. Interaction effects between dose and age, dose and start TSZ, and dose and start BMI-Z were also included.

The nature of the response to treatment and the effects of the variables mentioned above (independent variables) were assessed in a number of ways. Descriptive statistics were used for ΔTSZ and GVZ (first, second or third year) and independent variables. The proportion of poor responders, defined as those responding at <0·1, for ΔTSZ or GVZ was calculated. The combined effects of independent variables on ΔTSZ and GVZ were assessed by stepwise model 2 linear regression analysis. In the absence of a definitive interpretation of what an adequate response to GH treatment should be[20], we defined this to be the expected response given the optimization of those controllable variables identified as significant from the regression analyses. Given this definition, the overall response of the cohort was assessed. Distribution symmetry and linear relationships were assessed graphically. Distributions were tested for normality using the D'Agostino–Pearson omnibus test and appropriate tests used for comparisons of variables. Statistical

tests were performed using Microsoft Excel (Redmond, WA, USA) or SPSS 17.0 for Windows (Chicago, IL, USA).

Results

The effect of GH treatment was seen to increase the heights of this cohort of girls from approximately the mean (0·034 standard deviations above the mean) for Turner syndrome girls (Table 1) progressively over the 3 years of treatment to a median value of 1·46 standard deviations above the mean by the end of year 3.

Median ΔTSZ (Fig. 1) and GVZ values significantly decrease in each year of treatment despite the mean GH dose significantly increasing in each year (Table 1). There is also more variation in responses in the first year of treatment compared to the subsequent 2 years (Table 1). There was no significant difference between the first-year median ΔTSZ of those who went on to receive GH for a second year (ΔTSZ1 = 0·708) and those who did not (ΔTSZ1 = 0·639, $P = 0·623$). This was also the case for second-year response, with no significant difference between those going on to a third year of treatment (ΔTSZ2 = 0·459) and those not (ΔTSZ2 = 0·357, $P = 0·216$). Similar results as shown in Table 1 were seen when only those girls who received treatment in each of the 3 years were considered (Supplementary Table S1). For those girls completing 3 years of treatment, the median total ΔTSZ = 1·633 of which 48% was contributed by the first-year response and 28% and 23% from the second-and third-year responses respectively.

The percentage of poor responders as defined by $Z < 0·1$, for both ΔTSZ and GVZ, also increased each year: 9·1%, 12·1%, and 17·1% for ΔTSZ and 1·1%, 5·4%, and 9·4% for GVZ. Factors that were identified as being notably different between ΔTSZ poor responders and other patients are shown in Table 2. Of the 18 ΔTSZ poor responders identified in second year, 4 were also among the 16 poor responders in first year. Of the 20 poor responders in the third year, 3 were also poor responders in second year and 2 in first year. No individual was classified as a poor responder in all 3 years.

In Australia, the Department of Health and Ageing recommends GH dose to start at 4·5 mg/m^2/week with the provision to increase this to 7·5 mg/m^2/week and, for TS, to a maximum of 9·5 mg/m^2/week. As a consequence, three dose range groups were identified and these designated as Low, Medium, and High as defined in Table 3. The demographics of dose range groups and their effect on response are also shown in Table 3.

Defining dose range groups allows for an analysis of the effects of incremental dosing (Fig. 2 and Supplementary Table S2). Individuals moving to a higher dose range group from 1 year to the next generally had a significantly poorer response in the previous year compared to girls who remained in the same dose range group. Moving up a dose range group had the effect of significantly easing the general decline in response but not to improve on a poor response from the previous year (Fig. 2 and Supplementary Table S2).

Model 2 linear regression using a stepwise addition of variables was used to identify possible relationships between influencing factors for response in each year of treatment.

The linear regression model for ΔTSZ1 is shown below,

ΔTSZ1 = 0·087 (MeanDoseY1) − 0·001 (Age * DoseY1) + 0·099 (BMIZStartY1) − 0·111(TSZStartY1) + 0·140.

Thus, factors influencing ΔTSZ1 are mean dose in the first year of treatment and the BMI-Z and TSZ at the start of treatment.

Table 1. Median values for baseline data and response measures

	Treatment-year cohort			
	1st year	2nd year	3rd year	*P**
Number of patients	176	148	117	
Before starting GH				
Age† at start GH	5·8	5·5	5·3	0·234
Mean parent SDS‡	−0·163	−0·210	−0·186	0·989
At start of or during year of treatment				
TSZ Start	0·034	0·559	1·005	$1·44 \times 10^{-13}$
SDS‡ Start	−2·386	−2·043	−1·881	$1·50 \times 10^{-8}$
BMI§ (BMI-Z) Start	16·4 (0·385)	16·4 (0·356)	16·5 (0·522)	0·682 (0·622)
BA-CA Start¶	−0·803	−1·199	−0·798	0·686
Mean GH dose** during	5·5 (0·23)	6·4 (0·24)	7·2 (0·26)	$6·24 \times 10^{-4}$
Response measures (IQR††)				
ΔTSZ	0·705 (0·537)	0·439 (0·426)	0·377 (0·379)	$5·85 \times 10^{-11}$
GVZ	1·824 (1·335)	1·133 (0·855)	0·762 (0·698)	$1·10 \times 10^{-22}$
ΔSDS‡	0·406 (0·548)	0·194 (0·384)	0·097 (0·303)	$2·78 \times 10^{-16}$
TSZ End	0·641 (1·408)	1·003 (1·462)	1·461 (1·428)	$8·11 \times 10^{-8}$

BA, bone age; CA, chronological age; GH, growth hormone.
*P-value for Kruskal–Wallis test.
†Years.
‡Height standard deviation score from Centers for Disease Control tables for general population.
§kg/m^2.
¶Bone age minus chronological age in years.
**mg/m^2/week (mg/kg/week).
††Inter quartile range.

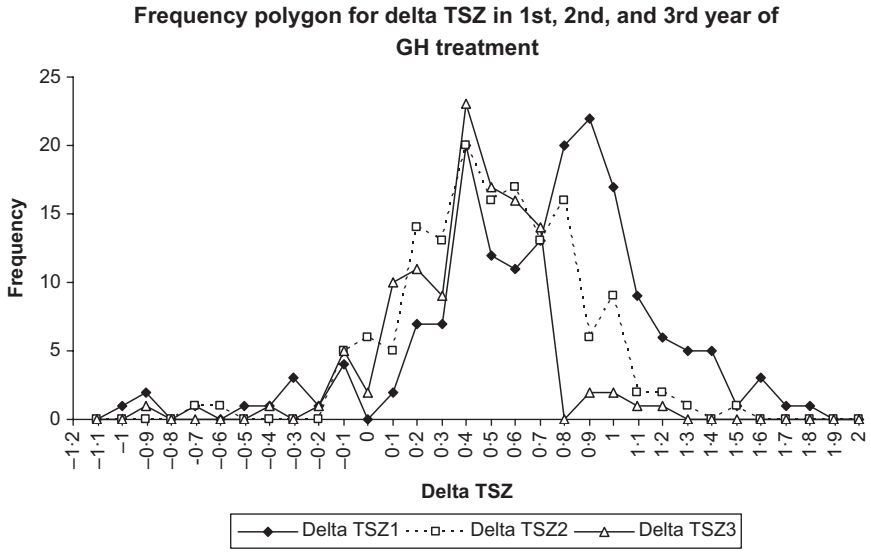

Fig. 1 ΔTSZ response to growth hormone treatment for each year of treatment.

Table 2. Percentage of poor responders as defined as ΔTSZ < 0·1 with notable differences between poor responders and others

Treatment year	Variable	*Z* < 0·1	Z > 0·1	P
1	%	9·1	81·9	
	GH dose*	4·3	5·7	0·0002
	BMI-Z	−0·5	0·5	0·003
	Age start†	2·5	6·1	$4{\cdot}4 \times 10^{-7}$
2	%	12·1	88·9	
	ΔTSZ1	0·42	0·73	0·02
	GH dose*	5·2	6·5	0·095
3	%	17·1	83·9	
	TSZ start	0·46	-0·24	0·004

GH, growth hormone.
*mg/m^2/week.
†Years.

Importantly, an interaction effect between age at start of treatment and mean dose is identified. Specifically, young children on high doses of GH respond disproportionately better than others. The interaction effect is demonstrated in Fig. 3 by the nonparallel nature of the regression lines for each dose level. No other factors among those listed previously were identified as significant.

The multiple R^2 for this model is 0·284, meaning it accounts for 28·4% of the variation seen in ΔTSZ1. The relative influence of each variable can be appreciated from the standardized regression coefficients, β, and the relative contribution to the total variance in ΔTSZ1 (%); $\beta_{MeanDoseY1} = 0{\cdot}412$ (13·1%), $\beta_{Age*Dose} = -0{\cdot}210$ (5·4%), $\beta_{BMIZstartY1} = 0{\cdot}272$ (4·1%), and $\beta_{TSZstartY1} = -0{\cdot}255$ (5·9%).

It is evident that both starting height and starting age – through the dose interaction effect – influence response. However, the two variables are correlated (Spearman Rank $r_{Age,TSZ} = 0{\cdot}272$,

Table 3. Median values of variables for dose range groups in each treatment-year cohort

Treatment year	Dose range group*	Dose†	*n* (%)	Age start growth hormone ‡	ΔTSZ	GVZ
1st	Low	4·6 (0·19)	70 (46·4)	4·47	0·57	1·53
	Medium	6·5 (0·26)	39 (25·8)	5·29	0·73	1·85
	High	8·8 (0·32)	42 (27·8)	8·65	0·90	2·13
	P	$\mathbf{8{\cdot}58 \times 10^{-29}}$		$\mathbf{3{\cdot}14 \times 10^{-6}}$	$\mathbf{6{\cdot}65 \times 10^{-5}}$	0·051
2nd	Low	4·7 (0·19)	44 (33·3)	4·24	0·42	1·15
	Medium	6·8 (0·27)	55 (41·7)	5·34	0·46	1·08
	High	8·6 (0·32)	33 (25·0)	7·44	0·54	1·23
	P	$\mathbf{1{\cdot}28 \times 10^{-25}}$		**0·001**	0·513	0·804
3rd	Low	4·8 (0·18)	24 (20·2)	5·68	0·31	0·74
	Medium	6·7 (0·26)	50 (44·2)	4·85	0·39	0·71
	High	8·6 (0·31)	39 (34·5)	5·95	0·40	0·81
	P	$\mathbf{1{\cdot}04 \times 10^{-21}}$		**0·014**	0·086	0·575

P-value for Kruskal–Wallis test. Bold if P < 0.05.
*Low: 4·00–5·49, Medium 5·50–7·99, High 8·00–9·99 mg/m^2/week.
†mg/m^2/week (mg/kg/week).
‡Years.

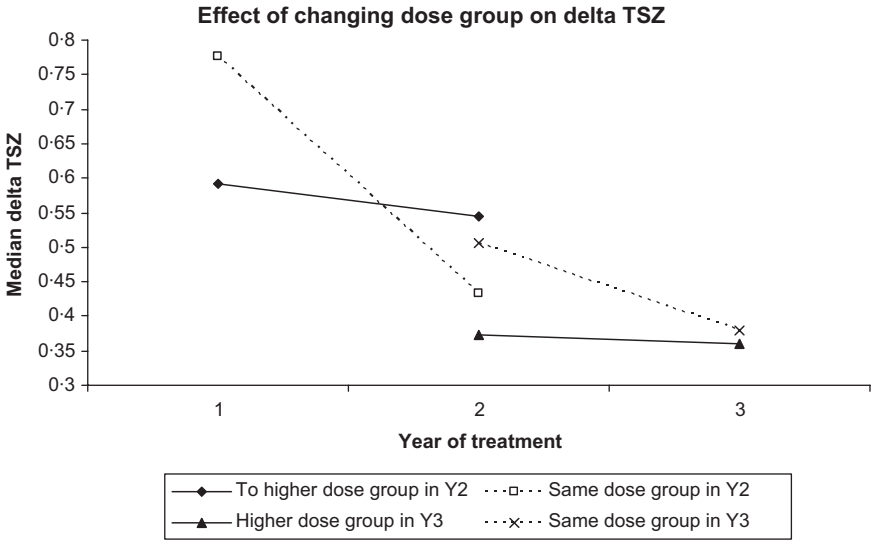

Fig. 2 Effect of changing to a higher dose range group on ΔTSZ response.

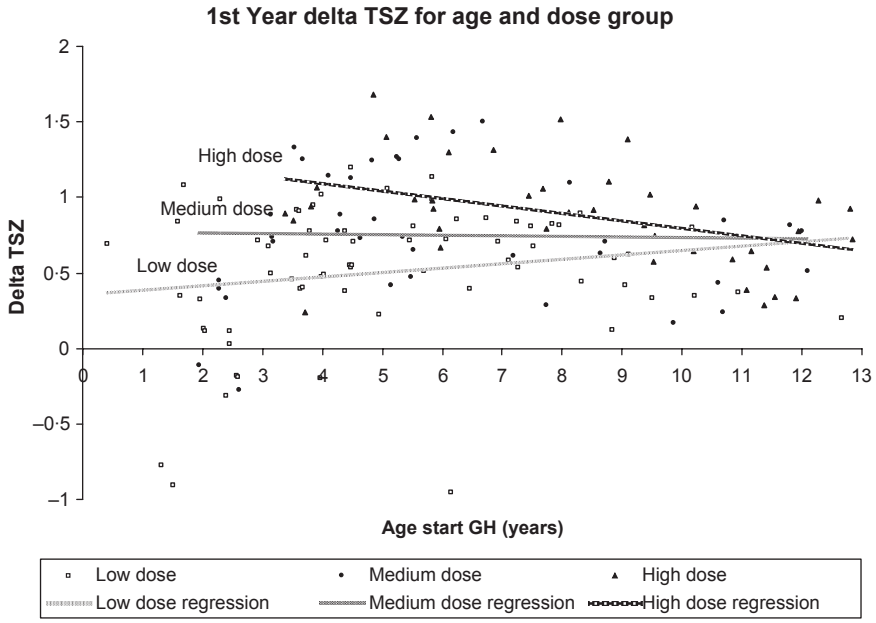

Fig. 3 Interaction effect between starting age and dose group on ΔTSZ in first year of growth hormone treatment.

$P = 2{\cdot}6 \times 10^{-4}$) as girls starting GH at a younger age also tend to be shorter. The complex nature of the relationship between starting age, starting height (TSZ), and response to GH treatment (ΔTSZ) is evidenced by the fact that starting height rather than age is identified in the regression equation while the Dose*Age interaction rather than a Dose*TSZ interaction is also identified.

In the second year of treatment,

$$\Delta TSZ2 = 0.168(\Delta TSZ1) - 0.001(Age^{*}DoseY2) + 0.328$$

$R^2 = 0{\cdot}128.\beta_{\Delta TSZ1} = 0{\cdot}245$ (8·7%) and $\beta_{Age^{*}Dose} = -0{\cdot}208$ (4·1%).

In the third year of treatment,

$$\Delta TSZ3 = -0.003(AgeStart) + 0.039(MeanDoseY3) + 0.308$$

$R^2 = 0{\cdot}092$. $\beta_{AgeStart} = -0{\cdot}297$ (5·8%), $\beta_{MeanDoseY3} = 0{\cdot}192$ (3·3%).

For the total response to GH treatment over the 3 years of treatment,

$$\Delta TSZ0-3 = 0.128(MeanDoseY1) - 0.003(Dose^{*}Age) - 0.146(TSZStart) + 0.787$$

Other variables included in this analysis but not identified as significantly contributing to the model were total mean dose, mean dose Y2, mean dose Y3, mean BMI-Z, and changes in dose range group. For this model, $R^2 = 0{\cdot}195$ with $\beta_{MeanDoseY1} = 0{\cdot}351$ (8·8%), $\beta_{AgeStart^{*}TotalDose} = -0{\cdot}248$ (7·1%), and $\beta_{TSZStart} = -0{\cdot}190$ (3·5%). The identification of the importance of first-year GH dose to total response is particularly noteworthy.

Regression equations were also constructed for GVZ and can be seen in the supplementary material associated with this study.

Clinically, it is important to define what might be considered an acceptable response. It is evident that an optimal response is primarily dependent upon a young age and high dose of GH in the first year of treatment. Thus, an acceptable response may be defined as that expected for a girl starting treatment at the median age (5·8 years) on a GH dose within the high dose range. Using the high dose regression line (Fig. 3, ΔTSZ1 = −0·05(Age) + 1·3) and the median age, an acceptable response may be estimated as ΔTSZ1 = 1·01. Only 31 of 176 (17·6%) girls achieved this response in the first year of treatment. While the total numbers are skewed towards low doses for young girls and high doses for older girls the importance of a young age and a high dose may be appreciated from Table 4.

Discussion

This report affords a unique insight into response to GH in TS patients as it reports on the first 3 years of patient response in a nationwide treatment program. It thus encompasses considerable variation in important parameters such as GH dose, age at commencement of treatment, initial height, BA delay, and karyotype. The data presented here identified a significant interaction effect between age at commencement and dose of GH in terms of ΔTSZ response (Fig. 3). Specifically, higher GH doses have a disproportionately beneficial effect at younger ages. This interaction effect was seen to be significant in the first and second years and in the total response over the 3 years of treatment. Age at commencement of GH treatment and dose are consistently identified in reports in which response models were built[9,11–13,21–26], but an interaction between the two has not previously been reported.

In the literature, factors reported to be positively associated with first-year height response to GH treatment of TS include weight SDS, mean parental height SDS, birth weight SDS, BMI, number of injections per week, use of oxandrolone, and dose of GH. Age and height SDS at GH commencement are negatively associated with response.[11,14,21,24–26] Similar factors have been found to be important in final height gained with, additionally, age at onset of puberty, duration of GH treatment, birth length, bone age delay, maternal X chromosome origin, and first-year height response identified as positive factors.[9–13,21,23,26] The most important factors positively influencing final height were a young age at GH commencement, a low BA-to-CA ratio at the start of treatment, and good first-year response to treatment.[9,12,13,21,23,26] The other important parameter affecting both first year and adult height outcomes was GH dose.[9,11,12,21,23,26] Interestingly, response to GH was not found to be associated with an individual's karyotype[12,26], which was also found to be the case in the present study.

As with previous studies,[9,11–13,21–26] our results show, in general, that younger, shorter girls on a higher GH dose with a larger BMI-Z respond best to GH in the first year. Bone age delay was not found to have a significant affect although not all individuals had BA recorded for the specific clinic visit being recorded, and thus sample size may have been too small. Poor responders essentially were found to have the opposite attributes, low dose and smaller BMI-Z except that, in contrast, they too were younger. This highlights the, almost universal, practice of starting young patients on a low dose and emphasizes the importance of the combination of young age and high dose on optimal response.

Growth response was seen to decrease significantly over the 3 years of treatment which is consistent with the previous observations.[1,11,14,20,21,23,27–29] However, dose received increased over the same period. The starting dose of 5·5 mg/m^2/week (0·23 mg/kg/week) was low by international standards (0·23–0·36 mg/kg/week).[4, 8–13] Despite this, the median first-year response (ΔTSZ = +0·705 or ΔSDS Height = +0·406) was comparable to other published first-year responses that vary from 0·35 to 1·0[12,13,21,22,26–30] for ΔTSZ and 0·3–0·66 for ΔSDS height[1,11–13,20,21,24,28]. The dose used in Australia fell into three distinct groups that were designated as low, medium, and high (Table 3). From a low starting dose, patients frequently 'moved up' a dose group in subsequent years. The effect of such dose increments (usually in reaction to a poor response in the previous year), while significant, only attenuated the normal decline in response (Fig. 2). Similar observations and conclusions have been made by other groups. A study of step-up dosage regimes published by van Pareren *et al.*[23] showed that although dose increment had a significant effect on final height, the effect was small and discernable only after 4–7 years. Conversely, Bertrand's group,[27] using a very low initial dose (0·15 mg/kg/week), found stepping up to 0·3 mg/kg/week did have a significant effect in the second year. In a study of children diagnosed with idiopathic short stature, Wit's group[31] concluded that there was an initial treatment effect. That is, that the dose given in the first year to a large extent set the final height outcome. This also seemed to be the case in the present study with first-year dose being identified as the most important influencing factor to total response over the 3 years. From van Pareren *et al.*'s[23] results and those presented here, when using typical starting doses (0·23–0·36 mg/kg/week),[4–6,8–13], it would appear that an initial treatment effect is also at play with respect to GH treatment of Turner syndrome.

This Australian cohort began GH treatment at a younger age (median = 5·8 years, mean = 6·5 years) compared to international (6·5–11·9 years)[8–13,20,21,23,24,26–29] or earlier Australian cohorts (9·2–10·6 years).[1,2] An older age at commencement of GH therapy has been shown to be a significant negative factor in first-year response and final height gained.[9,11–13,20–24,26,27,29,30,32] Thus, the young commencement age of the Australian cohort may account for the comparatively good response despite the low starting dose of GH. The observed interaction effect of age and dose amplifies the importance of not only commencing treatment at a young age but initiating at a high dose. Indeed, this study revealed that poor

Table 4. Proportions attaining a ΔTSZ1 > 1·01 with respect to starting age and dose range group

Dose range group	<5·8 years (%)	>5·8 years (%)
Low	4/43 (9·3)	1/27 (3·7)
Medium	8/24 (33·3)	3/15 (20·0)
High	3/8 (37·5)	9/34 (26·5)

responders in the first year not only received a lower GH dose but were also often younger, indicating that the low dose outweighed the benefit of a young starting age in some girls. More generally, it was shown that total response over the 3 years of treatment was compromised in the youngest girls as a consequence of the low GH dose initially received. Total response is highly associated with mean first-year dose and a more aggressive approach to dose in young TS girls in Australia is warranted; moving to higher doses later is not as efficient or as efficacious.

Growth centres around the world administer GH in terms of mg/kg or, as in Australia, milligram per metre square of BSA. There has consequently been interest and debate among paediatric endocrinologists and health economists as to which is most beneficial.[21,33] The result here, that an interaction effect of dose with age was detected when using milligram per metre square but that such an effect is not seen in studies in which weight based dosing is used, helps advance the debate. The fact that a milligram per metre square dose regime is associated with an additional benefit (the age*dose interaction) to response suggests that it is particularly suited, more so than mg/kg, to the treatment of younger patients.

An interesting question arises from the results of the present study. Is a young age or a short starting height of primary importance in predisposing to a good response to GH treatment in TS? The two are related in that those starting GH at a younger age are also, in general, shorter. However, despite this, the results presented here suggest that both may be important. An interaction effect with dose was identified with starting age but not with starting height while, conversely, it was starting height rather than starting age that was identified as a main effect in our regression analyses.

To identify what might be considered an acceptable first-year response, it was suggested that the response expected from a high GH dose at the median age (5·8 years) could provide such a bench mark. Using these criteria, an acceptable response was defined as approximately a 1 standard deviation increase in TS-specific height SDS in the first year. Only 17·6% of girls achieved this indicating considerable opportunity for improvement.

In summary, it is apparent from our review of the Australian GH treatment program for TS that the first year of treatment is particularly important as response is greatest and is most amenable to manipulation by dose variation. The effect of a dose increment after the first year cannot reverse the normal decline in response. It is also, as we demonstrated for the first time, when dose and age at commencement interact, with younger patients responding disproportionately better to higher doses. These factors, but in particular first-year dose, may also set the potential for response, possibly over the whole period of treatment. Our analysis supports initiating GH treatment of Turner syndrome as early as possible with the highest safe dose, at least 9·5 mg/m^2/week (0·39 mg/kg/week), in the first year.

Acknowledgements

We thank the participants and their carers for consenting to provide the clinical data used in this work. We also thank the treating paediatric endocrinologists and nurses for collection of this data. We acknowledge the Pharmaceutical Benefits Division of the Department of Health and Ageing for their support in the collection of GH treatment data.

Disclosure statement

IPH, MH, GRA, WSC, PLH, CTC, GW, AC, and PSWD have nothing to disclose. CSC has served on the OZGROW committee advising APEG.

References

1 Cowell, C.T., Dietsch, S. & Greenacre, P. (1996) Growth hormone therapy for 3 years: the OZGROW experience. *Journal of Paediatrics and Child Health*, **32**, 86–93.
2 Werther, G.A., Wang, M. & Cowell, C.T. (2003) An auxology-based growth hormone program: update on the Australian experience. *Journal of Pediatric Endocrinology and Metabolism*, **16**(Suppl. 3), 613–618.
3 Stratakis, C.A., Sarafogluou, K. & Miller, B.S. (2008) Chapter 31: Turner syndrome. In: K. Sarafoglou ed. *Pediatric Endocrinology and Inborn Errors of Metabolis*. McGraw-Hill: New York, pp. 477–486.
4 Baxter, L., Bryant, J., Cave, C.B. *et al.* (2007) Recombinant growth hormone for children and adolescents with Turner syndrome. *The Cochrane database of systematic reviews*, Jan 24; 1, CD003887.
5 Davenport, M.L. (2010) Approach to the patient with Turner syndrome. *Journal of Clinical Endocrinology and Metabolism*, **95**, 1487–1495.
6 Saenger, P., Wikland, K.A., Conway, G.S. *et al.* (2001) Recommendations for the diagnosis and management of Turner syndrome. *Journal of Clinical Endocrinology and Metabolism*, **86**, 3061–3069.
7 Rao, E., Weiss, B., Fukami, M. *et al.* (1997) Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. *Nature Genetics*, **16**, 54–63.
8 Blum, W.F., Cao, D., Hesse, V. *et al.* (2009) Height gains in response to growth hormone treatment to final height are similar in patients with SHOX deficiency and Turner syndrome. *Hormone Research*, **71**, 167–172.
9 Davenport, M.L. (2006) Evidence for early initiation of growth hormone and transdermal estradiol therapies in girls with Turner syndrome. *Growth Hormone & IGF Research*, **16**(Suppl A), S91–S97.
10 Hamelin, C.E., Anglin, G., Quigley, C.A. *et al.* (2006) Genomic imprinting in Turner syndrome: effects on response to growth hormone and on risk of sensorineural hearing loss. *Journal of Clinical Endocrinology and Metabolism*, **91**, 3002–3010.
11 Ranke, M.B., Lindberg, A., Chatelain, P. *et al.* (2000) Prediction of long-term response to recombinant human growth hormone in Turner syndrome: development and validation of mathematical models. KIGS International Board. Kabi International Growth Study. *Journal of Clinical Endocrinology and Metabolism*, **85**, 4212–4218.
12 Ranke, M.B., Lindberg, A., Ferrandez Longas, A. *et al.* (2007) Major determinants of height development in Turner syndrome (TS) patients treated with GH: analysis of 987 patients from KIGS. *Pediatric Research*, **61**, 105–110.
13 Soriano-Guillen, L., Coste, J., Ecosse, E. *et al.* (2005) Adult height and pubertal growth in Turner syndrome after treatment with

recombinant growth hormone. *Journal of Clinical Endocrinology and Metabolism*, **90**, 5197–5204.
14 Bakker, B., Frane, J., Anhalt, H. *et al.* (2008) Height velocity targets from the national cooperative growth study for first-year growth hormone responses in short children. *Journal of Clinical Endocrinology and Metabolism*, **93**, 352–357.
15 Lyon, A.J., Preece, M.A. & Grant, D.B. (1985) Growth curve for girls with Turner syndrome. *Archives of Disease in Childhood*, **60**, 932–935.
16 Australian-Government. (2007) Guidelines for the Availability of Human Growth Hormone (hGH) as a Pharmaceutical Benefit. [cited; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/B689FDCC64C2400ACA257170001B47CA/$File/HGHGuidelines_march2007.pdf]
17 Haeusler, G., Schemper, M., Frisch, H. *et al.* (1992) Spontaneous growth in Turner syndrome: evidence for a minor pubertal growth spurt. *European Journal of Pediatrics*, **151**, 283–287.
18 NHANES. (2008) *CDC Growth Charts: United States*. U.S. Department of Health and Human Services: Atlanta, G.A.
19 Mosteller, R.D. (1987) Simplified calculation of body-surface area. *New England Journal of Medicine*, **317**, 1098.
20 Ranke, M.B. & Lindberg, A. (2010) Observed and predicted growth responses in prepubertal children with growth disorders: guidance of growth hormone treatment by empirical variables. *Journal of Clinical Endocrinology and Metabolism*, **95**, 1229–1237.
21 Betts, P.R., Butler, G.E., Donaldson, M.D. *et al.* (1999) A decade of growth hormone treatment in girls with Turner syndrome in the UK. UK KIGS Executive Group. *Archives of Disease in Childhood*, **80**, 221–225.
22 Johnston, D.I., Betts, P., Dunger, D. *et al.* (2001) A multicentre trial of recombinant growth hormone and low dose oestrogen in Turner syndrome: near final height analysis. *Archives of Disease in Childhood*, **84**, 76–81.
23 van Pareren, Y.K., de Muinck Keizer-Schrama, S.M., Stijnen, T. *et al.* (2003) Final height in girls with turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. *Journal of Clinical Endocrinology and Metabolism*, **88**, 1119–1125.
24 Cutfield, W.S. & Lundgren, F. (2009) Insulin-like growth factor I and growth responses during the first year of growth hormone treatment in KIGS patients with idiopathic growth hormone deficiency, acquired growth hormone deficiency, turner syndrome and born small for gestational age. *Hormone Research*, **71**(Suppl 1), 39–45.
25 Geffner, M.E. & Dunger, D.B. (2007) Future directions: growth prediction models. *Hormone Research*, **68**(Suppl 5), 51–56.
26 Quigley, C.A., Crowe, B.J., Anglin, D.G. *et al.* (2002) Growth hormone and low dose estrogen in Turner syndrome: results of a United States multi-center trial to near-final height. *Journal of Clinical Endocrinology and Metabolism*, **87**, 2033–2041.
27 Bertrand, A.M., Chaussain, J.L., Job, B. *et al.* (1996) Three years of GH treatment in Turner's syndrome: complex effect of GH dosage on growth parameters. French Pediatric Clinics and Sanofi-Winthrop. *Clinical Endocrinology*, **44**, 665–671.
28 Menke, L.A., Sas, T.C., de Muinck Keizer-Schrama, S.M. *et al.* (2010) Efficacy and safety of oxandrolone in growth hormone-treated girls with turner syndrome. *Journal of Clinical Endocrinology and Metabolism*, **95**, 1151–1160.
29 Massa, G., Maes, M., Heinrichs, C. *et al.* (1993) Influence of spontaneous or induced puberty on the growth promoting effect of treatment with growth hormone in girls with Turner's syndrome. *Clinical Endocrinology*, **38**, 253–260.
30 Ranke, M.B., Partsch, C.J., Lindberg, A. *et al.* (2002) Adult height after GH therapy in 188 Ullrich-Turner syndrome patients: results of the German IGLU Follow-up Study 2001. *European Journal of Endocrinology*, **147**, 625–633.
31 Wit, J.M., Rekers- Mombarg, L.T., Cutler, G.B. *et al.* (2005) Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. *Journal of Pediatrics*, **146**, 45–53.
32 Reiter, E.O., Blethen, S.L., Baptista, J. *et al.* (2001) Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. *Journal of Clinical Endocrinology and Metabolism*, **86**, 1936–1941.
33 Wit, J.M. (2007) Optimizing growth hormone therapy in growth hormone deficient children: what to do in the absence of hard evidence? Commentary on Rachmiel *et al.*: final height in children with idiopathic growth hormone deficiency treated with a fixed dose of recombinant growth hormone (Horm Res 2007; 68: 236–243). *Hormone Research*, **68**, 244–247.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Statistical analysis.

Table S1. Response and mean dose in each year of girls who had completed 3 years of treatment.

Table S2. Changing to a higher dose range group: median response in previous year, current year, and median change in response.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.