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Original Article

Growth Hormone Regimens in Australia: Analysis of the First Three Years of Treatment for Idiopathic Growth Hormone Deficiency and Idiopathic Short Stature.

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Key Words

GH, Idiopathic GH deficiency, auxology.

Summary

Objective: To investigate response to growth hormone (GH) in the 1st, 2nd and 3rd years of treatment for all idiopathic GH deficient (GHD) and idiopathic short stature (ISS) patients in Australia.

Context: Eligibility for subsidised GH treatment in Australia is determined on auxological criteria for the indication of Short Stature and Slow Growth (SSSG) which includes ISS (SSSG-ISS). The biochemical GHD (BGHD, peak GH<10mU/L) and SSSG indications are treated similarly: starting dose of 4.5mg/m^2/week with provision for incremental dosing. Some ISS patients were specifically diagnosed with familial short stature (SSSG-FSS).

Design: Responses for each year of treatment for BGHD, SSSG-ISS, and SSSG-FSS cohorts were compared in relation to influencing variables and with international benchmarks. The effect of incremental dosing was assessed.

Patients: Australian BGHD, SSSG-ISS, and SSSG-FSS patients who had completed one, two, or three years of treatment and were currently receiving GH.

Measurements: GH dose, change in height standard deviation score (ΔSDS), and growth velocity (GV).

Results: First year response was two to three times greater than that in subsequent years: $\Delta SDS_{1st\ Year}$=0.92, 0.50, and 0.46 for BGHD, SSSG-ISS, and SSSG-FSS respectively. Responses were similar to international reports and inversely related to age at commencement of GH. First year GV-for-age for BGHD patients was similar to international standards for idiopathic GHD. However, girls had an inferior response to boys when treatment commenced at less than 6 years of age. First year GV-for-age for SSSG-ISS/FSS patients was less than ISS standards. Dose increments attenuated the 1^{st}-to-2^{nd} year decline in response for BGHD but marginally improved responses for SSSG-ISS/FSS.

Conclusions: The Australian auxology based GH program produces comparable responses to international programs. A lower starting dose is offset by initiation of treatment at younger ages. Incremental dosing does not appear optimal. A first year dose of 6.4-6.9mg/m^2/week for GHD and 8.9mg/m^2/week for ISS with early commencement of GH treatment may be most efficacious.

Introduction

The growth hormone (GH) treatment program in Australia is subsidised by the Commonwealth Government's Department of Health and Ageing (DoHA) through the Pharmaceutical Benefits Scheme (PBS) and differs significantly from most other GH prescribing jurisdictions around the world. The most notable differences are the extensive use of auxological assessment, dosing in mg/m^2 rather than mg/kg, a low, by international comparison, GH starting dose of 4.5mg/m^2/week (1-5), (6, 7), and the provision to increment the dose at 6 monthly intervals (8).

Patients are assessed relative to set eligibility criteria for a number of specified indications. The two most common indications, and the focus of this study, are "biochemical GH deficiency" (BGHD) and "short stature and slow growth" (SSSG). BGHD and SSSG eligibility are defined below. Eligibility for GH under the SSSG indication is unique in that it is based solely on auxological criteria: Height less than the 1st centile with growth velocity less than 25th centile for skeletal age and sex(9). Demographic, treatment, and response data for all patients treated through the PBS is stored in the national paediatric GH database, OZGROW.

To compare the efficacy of the Australian system to others it is necessary to look at specifically recognised international diagnoses. In this study we concentrate on idiopathic Growth Hormone Deficiency (GHD) and Idiopathic Short Stature (ISS). The Australian indication of BGHD aligns with the internationally recognised diagnosis of idiopathic GHD. SSSG, as might be

expected given its auxological definition, contains within it a number of different diagnostic entities. A specific diagnosis for each patient, as determined by their paediatric endocrinologist, is recorded in OZGROW. Patients diagnosed as ISS by a paediatric endocrinologist form a sub-group within the SSSG indication and are referred to as SSSG-ISS in this study. The consensus statement on the diagnosis and treatment of children with ISS (1) defines a sub-category of ISS as familial short stature (FSS). Some paediatric endocrinologists have used this sub-categorization of ISS as their diagnosis and this group, SSSG-FSS, has been treated separately in this study.

This study involves a retrospective analysis of an entire national cohort of idiopathic GHD and ISS patients treated with GH. As such it is not a controlled experiment but rather a snap-shot of an ongoing program. In certain circumstances data that would be desirable is not available for all patients. These cases are noted and appropriate allowances made regarding results.

Response was assessed primarily using change in height standard deviation score, ΔSDS, in the first, second, and third years of treatment. First year response is known to be highly correlated with adult height in both GHD and ISS (4, 10-12). First year response was compared to international benchmarks and ΔSDS compared with response with respect to age of treatment commencement graphs published by Bakker *et al.*(13). Growth velocity (GV) was also calculated for comparison with the recent

comprehensive work on GV response to GH by Bakker *et al.*(13). Finally, factors influencing response were identified.

For comparison purposes each patient's dose in terms of mg/m^2 was converted to the equivalent mg/kg dose. It should be noted however that there is no simple generic conversion formula as the mg/m^2 dose depends on both the weight and height of the patient at the time of treatment. The efficacy of incremental dosing in a national program is also addressed and follows other studies that have questioned the practice (14-16). Cowell *et al.*(17), 1996 and Werther *et al.*(18) 2003 have previously reported on the Australian program and it is timely to update an assessment in an international context.

Materials and Methods

Indications for Subsidised GH Treatment

To receive subsidised GH for BGHD or SSSG patients must satisfy specific eligibility criteria (8). SSSG: Height less than the first centile (CDC Growth Charts(19)) with growth velocity less than 25th centile for skeletal age and sex(9). BGHD: Short stature (< 1st centile) with peak serum GH concentration ≤10mU/L (3.3ng/ml) in response to two stimulation tests or one test and other evidence of GH deficiency (8). The BGHD indication does not include those patients who have been treated with irradiation or who have an identified cranial lesion.

Dose can be incremented at 6 monthly intervals but only if patients fail to respond according to one or more of the response criteria defined in the DoHA guidelines(8). These are, a) GV>50th centile for bone age, b) ΔSDS>0, and c) GV>4cm/year.

Subjects

All children receiving GH as part of the Australian Government's PBS are recorded and their treatment monitored through DoHA. Basic demographic and clinical information is collected on each patient at each visit and recorded in 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 with each patient allocated an OZGROW number. Patients were selected who were recorded as currently receiving GH as of 3rd December 2007, had made at least one visit to a growth clinic in 2007, had received GH for at least 39 weeks in each year of treatment, and for which GH dose was available at each visit. Children in this group commenced GH treatment between 1994 and 2007. The numbers of patients, boys and girls, from each indication included in the study are shown in Table 1.

Measurements

Height, weight, age, and dose 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 values using the LMS procedure and the United States Growth Charts of the Centers for Disease Control and Prevention(CDC)(19). Height (Ht) and weight (Wt) measurements were used to estimate body surface area (BSA) using Mosteller's(20) formula $BSA(m^2) = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$. When heights of both parents were available, mean parental height-SDS could be calculated: $Ht(SDS)_{Mean-parent} = \frac{Ht(SDS)_{Father} + Ht(SDS)_{Mother}}{2}$. Bone ages were calculated using the method of Greulich and Pyle(21). Bone age delay (chronological age minus bone age) was recorded if the date on which bone age (BA) was observed was within 90 days of the GH treatment start date or last treatment date of a year. It is possible that a small number of patients entered puberty during the first three years of their treatment which would have influence their response to treatment. However, as accurate pubertal stageing was not available for all patients at every visit it was impossible to identify all those entering puberty for removal from the study. Simulations suggested removal of potentially pubescent patients would make little difference to overall results.

Analyses

Response Variables

Change in height-SDS (ΔSDS) for the 1st, 2nd, and 3rd years of GH treatment was used as the primary response variable. GV-SDS (GV-Z) was used as an alternative response variable. In practice, the visit closest to being 52 weeks since the commencement of GH or the last treatment date of the previous year was identified and the response normalized to 52 weeks. GV-Z was

calculated based on a comparison to CDC height standards(19) (medians for age) and the height velocity curves of Tanner and Davies(9). GV is also presented so that, in concert with age, comparisons could be made to the first year GV response standards of Bakker et al. (13). First year ΔSDS response with respect to age at treatment commencement was plotted and incorporated a moving mean of 20 individuals.

Determination of Successful Response

The consensus statement on ISS (1) recommends that a successful first year response to GH should be a ΔSDS of 0.3-0.5 or a GV-Z >1.0. First year ΔSDS for the BGHD cohort was compared to Bakker *et al.*'s (13) graph of first year ΔSDS (mean +/- SD) for idiopathic GHD as a function of treatment commencement age. First year GVs for girls and boys were plotted with respect to age of treatment commencement and compared to mean+/-SD curves from Bakker et al. (13). The number of patients responding above and below the mean of Bakker were compared to that expected using a Chi Square goodness of fit test.

Comparison of Those Patients who are Treated in Subsequent Years and Those who are Not.

While many patients are recorded only in the first year cohort because it is their current, and only, year of treatment it is possible that others drop out of the program. It would be useful, therefore, to identify differences between that group of patients who go on to subsequent years of treatment and those who do not.

The Effect of Dose Increment

Patients usually start GH treatment at 4.5mg/m^2/week but this dose may be increased by 1mg/m^2/week increments at minimum six month intervals from commencement of treatment. Annual mean dose may vary from year to year due to growth and dose adjustments for growth but an increase of 1mg/m^2/week is large in this context and may be interpreted as being due to a dose increment. If the difference in mean annual dose from one year to the next for an individual was more than 1mg/m^2/week this patient was defined as having had a dose increment.

Regression Analysis

Model 2 linear regression was used to identify variables that significantly affected ΔSDS in each year of treatment. A number of independent variables were investigated with regards to their potential influence on ΔSDS response to GH treatment. These were, before treatment commencement: age (months) at commencement, gender, birth weight, birth length, mean parental height-SDS, and Peak serum GH. At the beginning of each year of treatment or during that year: height-SDS, mean GH dose over the 52 weeks (mg/m^2/wk), BA delay, and body mass index (BMI, kg/m^2)-SDS (BMI-Z). In addition, the previous year's response was included as a factor and interaction effects between age and dose (age*dose) and between BMI-Z and dose (BMIZ*dose) were also investigated.

Distributions were tested for normality using the D'Agostino-Pearson omnibus test. Distribution symmetry and linear relationships were assessed graphically. For consistency, nonparametric tests were used routinely. Statistical tests were performed using Microsoft Excel or SPSS 18.0 for Windows.

Results

The study included 186 BGHD, 154 SSSG-ISS, and 56 SSSG-FSS patients. Baseline demographics are shown in Table 1 and Supplementary Tables 1 and 2. As expected, SSSG-FSS patients' parents were found to be significantly shorter than other ISS parents ($P=6.6\times10^{-6}$). SSSG-FSS patients also commenced GH treatment at a younger age than other ISS patients (this was significant when analysed with respect to the 3rd year cohort, P=0.02). Influencing variables that change with time (eg GH dose) and measures of response are shown in Table 2 and Supplementary Tables 1 and 2. Mean dose increased over the three years of treatment for SSSG-ISS and SSSG-FSS but remained at near starting levels for BGHD, even decreasing slightly in 2nd year. Response to treatment over the three years is shown in Figure 1.

Measures of Response

From Figures 1 and Tables 2 and Supplementary Table 1 it is clear that the highest ΔSDS response is seen in the first year of treatment and that it declines thereafter with the second and third year ΔSDS values being similar. First year ΔSDS response, with respect to age at commencement of GH

treatment is shown in Figure 2. In all cases a younger age is seen to be associated with a better response. For BGHD it was found that boys responded significantly better than girls (P=0.02) when starting treatment at less than 6 years of age. Boys' and girls' mean responses are shown separately for BGHD in Figure 2A. Mean dose in each of the three years was similar for BGHD but increased for SSSG-ISS and SSSG-FSS.

Comparisons to Recommended Benchmarks for First Year Response

Percentages of patients responding at less than the first year response benchmarks recommended by the consensus statement on ISS (1) are shown in Table 3. Figure 3 shows first year GV response in comparison to the standard curves of Bakker et al. (13). For the age range covered by the Bakker curves, more patients responded below Bakker's mean than expected. For BGHD this number approached significance for girls (P=0.06) but not for Boys (P=0.30). Comparing BGHD boys and girls younger than 6 years of age, girls GVs were significantly further from the Bakker mean than were the boys GV's (P=0.04). For SSSG-ISS and SSSG-FSS significantly more patients respond at less than Bakker's mean (ISS Girls: P=0.002, ISS Boys: $P=1.9\times10^{-5}$, FSS Girls: P=0.007, FSS Boys: $P=1.4\times10^{-5}$). Bakker et al.(13) suggested that patients responding at less than the mean GV-1SD should be considered poor responders. The percentages of patients considered poor responders under this criterion are shown in Table 3.

Comparison of Those Patients Who Were Treated in Subsequent Years and Those Who Were Not.

In general patients who did not receive a second year of treatment (treated in 1st year only) were older at GH commencement and had a poorer first year ΔSDS-Height compared to those who did (1st and 2nd or 1st, 2nd, and 3rd years). This was also the case for those who did not complete three years of treatment (1st, or 1st and 2nd years) compared to those who did (see supplementary Table 3).

The Effect of Dose Increment

The effect of dose increment on ΔSDS-Height for BGHD, and SSSG-ISS and SSSG-FSS patients can be seen in Figure 4. Values of ΔSDS-Height, change in ΔSDS-Height, and P-values of differences appear in Supplementary Tables 4 and 5. Those receiving a GH dose increment usually had a significantly inferior response in the previous year. The exception was BGHD patients and SSSG-FSS patients receiving a dose increment in third year. For the BGHD patients the effect of a dose increment in the second year was to attenuate the normal decrease in ΔSDS-Height from first to second year. Dose increments however lead to improved responses in the second year for SSSG-ISS and SSSG-FSS patients. Dose increments in the third year resulted in a significantly improved ΔSDS-Height for SSSG-ISS patients, marginally improved for BGHD, but only attenuated the decline for SSSG-FSS.

Regression Analyses

Model 2 linear regressions were employed using a stepwise addition of variables. A younger age at GH commencement was identified as being a significant influencing factor in first year response for each of BGHD, SSSG-ISS, and SSSG-FSS. Dose, somewhat counter intuitively, was found to be negatively associated with response in some instances as dose was only increased in reaction to a poor response. Full details of regression equations are shown in Supplementary Table 6.

Discussion

This report represents a complete national cross sectional audit of all GHD (BGHD) and ISS (SSSG-ISS and SSSG-FSS) patients ascertained in Australia using standardised eligibility and diagnostic criteria. As this is not an experimental population, trends in treatment or cessation of treatment and response with respect to demographic data and previous response can be assessed in a real clinical setting. Both SSSG and BGHD patients are initiated on a standard GH treatment protocol with the possibility of dose increments at 6 month intervals. As all patients were started on a low dose (4.5mg/m^2/week) the situations prompting, and the effect of, incrementing dose could be assessed in detail.

The BGHD and SSSG-ISS cohorts were demographically different with respect to most variables but similar with respect to gender ratio (Table 1). BGHD patients were younger, taller, and had a much larger BMI-Z at commencement of GH treatment than SSSG-ISS patients. SSSG-FSS

patients also commenced GH treatment at a younger age than other ISS patients, possibly reflecting the awareness of short stature in their parents. Given the similarity in dose it is not surprising that the BGHD patient cohort response was much superior to that of the SSSG-ISS/FSS cohorts.

The Australian median first year response of ΔSDS=0.50 for SSSG-ISS, and 0.46 for SSSG-FSS, compares well with two ISS cohorts described by Ranke et al (4) where median ΔSDSs for the first year were recorded as 0.52 and 0.4. Wit et al. (14) demonstrated a first year response of ΔSDS≈0.7 for "low dose" (0.24mg/kg/wk or approximately 6.7mg/m^2/wk) but 0.9 for "high dose" (0.37mg/kg/wk, ≈10.5mg/m^2/wk) GH treatment. In 1996 Cowell et al.(17) reported ΔSDS≈0.5 for the first year response in Australian ISS patients.

The first year ΔSDS of 0.92 reported here for BGHD also compares favourably with other reported responses for idiopathic GHD which range between 0.7 and 1.04 (10, 22-26). Cutfield and Lundgren(27) observed median ΔSDS of 0.7 to 0.9 from KIGS patients depending on IGF-1 response and whether GHD was idiopathic or acquired.

Responses to GH from this Australian cohort were achieved despite the mean first year dose (GHD: 4.27mg/m^2/week, SSSG-ISS: 4.63mg/m^2/week, SSSG-FSS: 4.57 mg/m^2/week, approximately equivalent to 0.17, 0.18, and 0.19mg/kg/week) being low by international comparison where reported doses range from 0.18 to 0.70mg/kg/week (1, 4-7, 11-14, 24, 25, 27-30). Wit (31) has suggested a dose of 6.4-6.9mg/m^2/week to be optimal for GHD. It is likely

that the reason for the similarity in response, despite a lower mean dose, is the younger median age of commencement of GH treatment in Australia. Commencement age in the present study is 5.1 years for BGHD, 8.2 years for SSSG-ISS, and 6.6 years for SSSG-FSS which is considerably younger than mean/median ages reported in international studies; GHD: 6.6-9.3years (10-12, 22-26, 28-30, 32) and ISS: 7.8-11.9years (3-5, 14, 24)). This hypothesis is supported by work by Bang et al. (33) who recently published a first year ΔSDS of 0.64 for ISS patients who received a starting dose similar to that reported here in Australia (0.22mg/kg/week) but who began treatment at an even younger age (7.0 years).

A young age at commencement of GH treatment was shown to be one of the most influential factors on ΔSDS in first year, and subsequent years, for both BGHD and ISS in this study and previous studies (1, 4, 11, 12, 22-24, 26, 28, 29, 32, 34, 35). This relationship has been shown specifically for both GHD and ISS by Bakker et al.(13) and Ranke's group (4, 26, 28).

More insight into the influence of age of GH commencement is gained from our comparison of response as a function of starting age with the GV and ΔSDS curves of Bakker et al.(13) (Figures 2 and 4). Bakker et al.'s (13) idiopathic GHD and ISS cohorts were started on doses almost twice that (0.30 mg/kg/wk) of those used in Australia (0.17mg/kg/wk for BGHD and 0.18-0.19mg/kg/wk for ISS). First year SSSG-ISS and SSSG-FSS responses were seen to be significantly inferior to Bakker et al.'s(13) ISS cohort. However, the BGHD patient's response was only marginally less that seen in Bakker's(13)

idiopathic GHD cohort suggesting that the Australian starting dose of 4.5mg/m^2/week (0.18mg/kg/week) is close to optimal for GHD, at least for boys, but too low for ISS. Indeed, a slightly higher dose of 0.23mg/kg/week for idiopathic GHD has been shown to achieve a mean adult height within the normal Swedish height range(35). Achievement of adult height is the ultimate goal of GH treatment and has been shown to be both dose dependent(36) and highly correlated with first year responsiveness(4) for ISS patients.

The observation that BGHD girls' first year response was significantly less than boys' when commencement age was younger than 5 or 6 years of age is noteworthy. This was seen both in terms of ΔSDS as a function of starting age and when GVs were compared to Bakker et al.'s(13) mean GV for starting age and sex. It is well known that there is a sexually dimorphic response to GH therapy in adults(37) but Rose et al. (38) demonstrated that in terms of Δ height SDS and GV-SDS gender did not influence prepubertal GH response at doses of 0.25-0.35mg/kg/week. It is likely, therefore, that the differential response noted here has been revealed as a consequence of the lower dose used and that response was measured specifically in relation to commencement age. That is, young GHD girls require a dose higher than 4.5mg/m^2/week (0.18mg/kg/week) to respond equivalently to boys of the same age.

An attempt was made to quantify poor response and first year response benchmarks from both the ISS consensus statement(1) and those suggested by Bakker et al.(13) were used. While Bakker et al.'s (13) mean -1SD

criterion is more useful as it covers most indications for GH and takes into consideration age at commencement both sets of benchmarks are essentially arbitrary. It is difficult to compare poor response rates to other studies as few give variance estimates but, at least for ISS, the poor response rate in Australia is concerning. The fact that poor response was associated with a discontinuation of treatment amplifies the importance of ensuring adequate response early.

One of the important and unique aspects of this study was the analysis of the use and effect of incremental dosing. All children in the study were nominally started on 4.5mg/m^2/week GH which could be incremented in 1mg/m^2/week steps following a poor response as specifically defined in the guidelines. Because of this protocol GH dose was, somewhat counter-intuitively, identified as a negative correlate with response in Australia. For BGHD patients a dose increment from first year to second year only attenuated the decline to a poorer second year response. A small improvement in response was seen, however, when the dose increment occurred from second year to third year for BGHD patients. SSSG-ISS patients receiving a dose increment showed improved response in all instances although in third year a dose increment did not improve the response of SSSG-FSS patients.

The literature suggests the practice of increasing an initial low dose may have little effect on height outcome. Wit *et al.*(14) have shown that an incremented (0.24mg/kg/week to 0.37mg/kg/week) cohort of ISS patients did not respond significantly better than a low dose group (0.24mg/kg/week) either over a two

year period or to the achievement of adult height. This was despite the low dose being used only in the first year of up to eight years of treatment. The high dose group (0.37mg/kg/week) produced significantly better responses to the other two groups. A similar conclusion was reported by van Pareren(39) with respect to GH treatment of Turner syndrome patients. It is possible that the positive effect of incremental dosing reported here reflects the particularly low initial doses used in Australia.

It can be concluded, from the results presented here, and from other studies (1, 4, 10-12, 14, 15, 22-24, 26, 28, 29, 31, 32, 34-36, 40) that optimal response, over both the short and long term, for GHD and ISS can be achieved by initiating GH as early as possible. By comparing first year response as a function of starting age to the curves published by Bakker(13) we conclude that the Australian starting dose (4.5mg/m^2/week ≈ 0.18mg/kg/week) is low to adequate for GHD but certainly too low for ISS. This assessment for GHD is in agreement with the recommendations of the Lawson Wilkins Pediatric Endocrine Society (approx. 5.6-10.5mg/m^2/week) (41) and Wit (6.4-6.9 mg/m^2/week) and follows the conclusions of Sas *et al.* (40) who recently compared low (4.9mg/m^2/week) and high (9.8mg/m^2/week) doses of GH in the treatment of GHD. It has been recognised that higher doses of GH are required in ISS patients to achieve similar responses and IGF-1 levels to those seen in GHD(10, 42). The Consensus Statement on ISS reports doses from 0.30 to 0.49mg/kg/week have been used in the treatment of ISS while Cohen et al.(42) found a dose of 0.83mg/kg/week was required to maintain an IGF-1 Level of +2SDS. As the Australian starting dose for ISS

was 0.18mg/kg/week it is not surprising that responses were found to be significantly below that of Bakker et al.'s(13) response for age standards. Given the importance of dose and first year response on adult height achievement it would also appear false economy to start with low doses and react to poor response by incremental dosing. Recent studies have also suggested that dose may be individualized, even from the first year of treatment, based on predictive models(10, 26).

Despite initial doses being only 65-70% of the range suggested by Wit (31) for GHD and 37-60% of that described in the Consensus Statement for ISS(1), median responses seen from the Australian GH program are similar to those reported in the literature for GHD and ISS patients. This is largely due to the generally younger median age at GH commencement seen in Australia, as when starting age was taken into consideration the ISS patients in particular were seen to respond comparatively poorly. The primarily auxology-based approach may allow a more expeditious processing of GH eligible children when compared to programs based on GH secretion testing allowing for younger GH commencement (18). Our findings suggest an optimal strategy would be to combine a first year GH dose of at least 6.4-6.9mg/m^2/week (≈0.23mg/kg/week) for GHD and 8.9mg/m^2/week (≈0.35mg/kg/week) for ISS, as commonly used internationally, with early commencement of treatment, as is the case in Australia.

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Table 1. Baseline demographics (first year cohort): Medians (IQR).

1st Year Cohort	BGHD	SSSG	
		ISS	FSS
Patients (Boys:Girls)	186 (123:63)	154 (108:46)	56 (33:23)
Age Starting GH (yrs)	5.11 (8.98, 2.06)	8.20 (10.79, 5.33)	6.60 (8.58, 5.03)
HtSDS at Start GH	-2.78 (-2.01, -3.51)	-2.99 (-2.63, -3.45)	-2.92 (-2.52, -3.23)
Peak Serum GH (µg/L)[1]	1.9 (2.85, 1.00)	9.0 (12.56, 7.00)	6.9 (10.93, 5.58)
Mean Parent HtSDS[1]	-0.18 (0.38, -0.57)	-0.72 (-0.22, -1.06)	-1.32 (-0.80, -1.73)
Birth Weight (kg)[1]	3.46 (3.75, 3.16)	3.03 (3.40, 2.54)	2.90 (3.12, 2.72)
Birth Length (cm)[1]	50 (51, 48)	48 (50, 47)	49 (50, 46.5)
Bone Age Delay (yrs)[1]	1.31(2.00, 0.50)	1.83 (2.65, 0.79)	1.69 (2.27, 0.85)

1. Not measured for all patients (See supplementary Tables 1 and 2).
IQR- interquartile range (3rd Quartile, 1st Quartile)

Table 2. Response data and yearly influencing variables (medians).

	BGHD			SSSG					
	Treatment Year Cohort			ISS-Treatment Year Cohort			FSS-Treatment Year Cohort		
At Start of or in Year	1st Year	2nd Year	3rd Year	1st Year	2nd Year	3rd Year	1st Year	2nd Year	3rd Year
HtSDS start	-2.78	-1.77	-1.24	-2.99	-2.52	-2.18	-2.92	-2.44	-2.08
BMI-Z start	0.46	0.34	0.30	-0.47	-0.59	-0.48	-0.15	-0.23	-0.28
Mean GH dose[1]	4.27(0.17)	4.07(0.16)	4.29(0.16)	4.63(0.18)	4.84(0.18)	5.62(0.20)	4.57(0.19)	4.78(0.19)	5.19(0.20)
Dose variation[2]	4.6-3.9	4.5-3.6	5.0-3.6	5.0-4.4	5.9-4.2	6.3-4.5	5.2-4.3	6.2-4.2	5.9-4.4
Previous Year's ΔSDS	-	0.94	0.32	-	0.57	0.25	-	0.49	0.32
Response									
ΔSDS (IQR)[3]	0.92	0.32	0.30	0.50	0.24	0.25	0.46	0.32	0.15
	(1.39, 0.47)	(0.62, 0.06)	(0.51, 0.02)	(0.74, 0.32)	(0.42, 0.09)	(0.35, 0.10)	(0.61, 0.29)	(0.41, 0.18)	(0.25, 0.06)
GV-Z (GV cm)	2.86(10.9)	0.83(7.6)	0.70(7.4)	1.91(7.9)	0.54(6.6)	0.69(6.5)	1.65(7.9)	0.76(6.6)	0.12(6.1)
Bone Age Delay (Yrs)	1.23	1.27	1.14	1.93	1.86	1.63	1.45	1.56	0.99

1. Median of individuals' mean dose throughout year in mg/m^2/week (mg/kg/week).
2. 3rd Quartile-1st Quartile (Interquartile Range) mg/m^2/week.
3. IQR- interquartile range (3rd Quartile, 1st Quartile).

Table 3. Percentages of children responding at less than specified first year response benchmarks.

ISS Consensus[1]	ΔSDS<0.3		ΔSDS<0.5		GV-Z<1.0	
	SSSG-ISS	SSSG-FSS	SSSG-ISS	SSSG-FSS	SSSG-ISS	SSSG-FSS
	21.6	30.4	51.0	53.6	29.8	35.7
Bakker GV Standards[2]	GV< GV Mean-1SD					
	BGHD		SSSG-ISS		SSSG-FSS	
	Girls	Boys	Girls	Boys	Girls	Boys
	21.4	13.8	26.7	26.4	21.7	33.3

1. Benchmarks recommended from the Consensus Statement on ISS (1). ΔSDS refers to the change in height SDS. GV-Z is the growth velocity SDS.
2. Curves of GVs for age of GH commencement for each gender and diagnosis according to Bakker et al.(13). To coincide with Bakker et al.'s(13) curves only individuals commencing GH treatment between the ages of 2 and 14 years were considered.

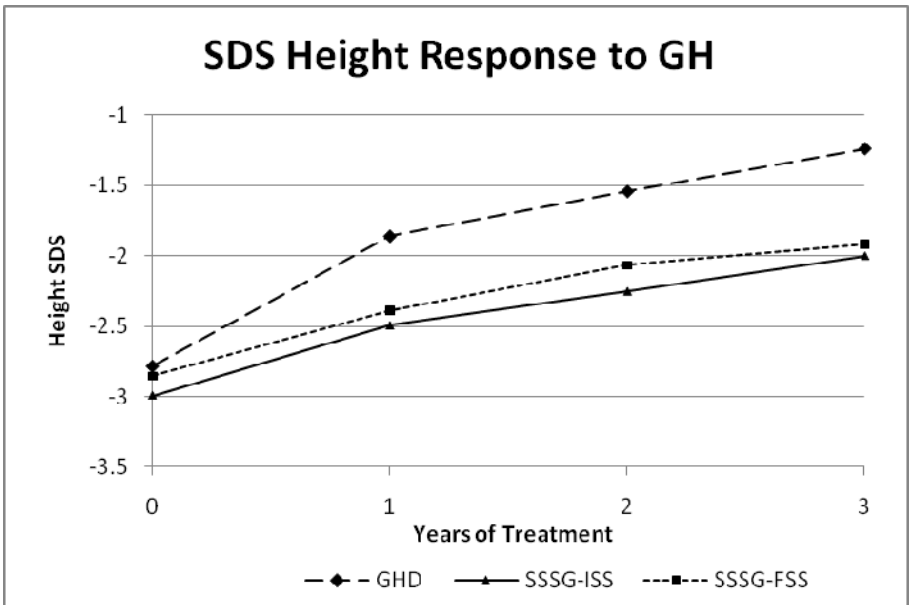
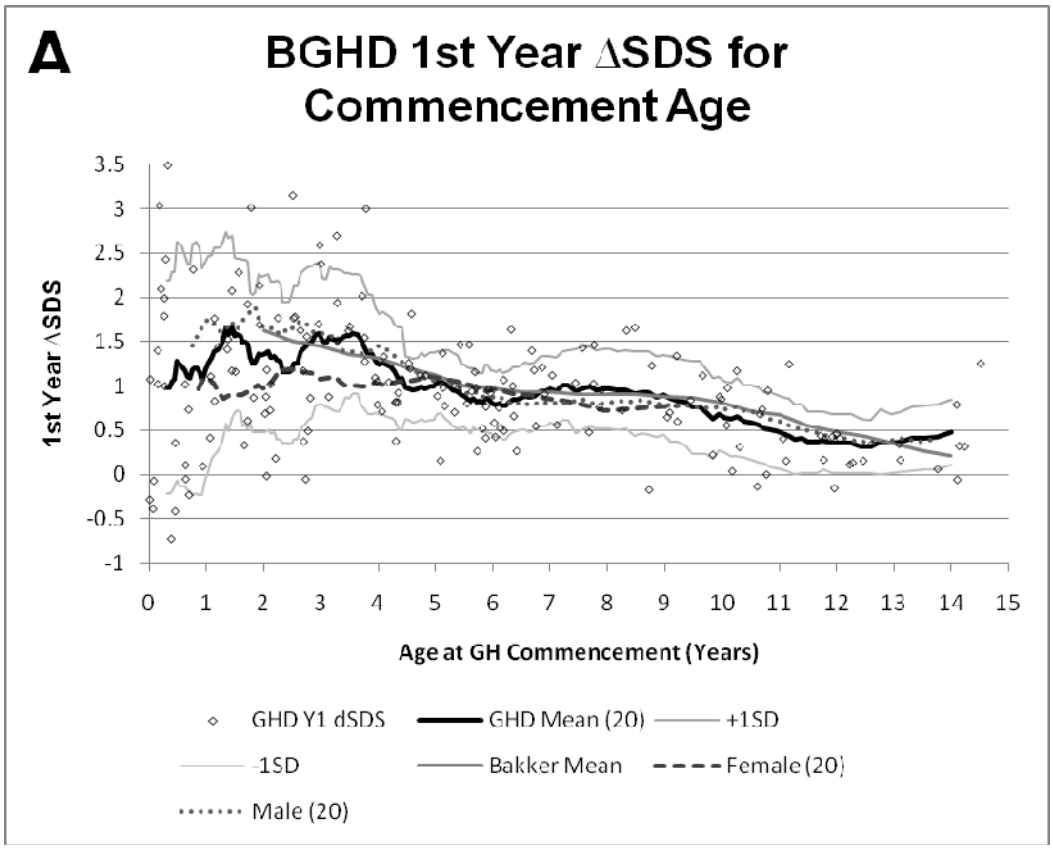
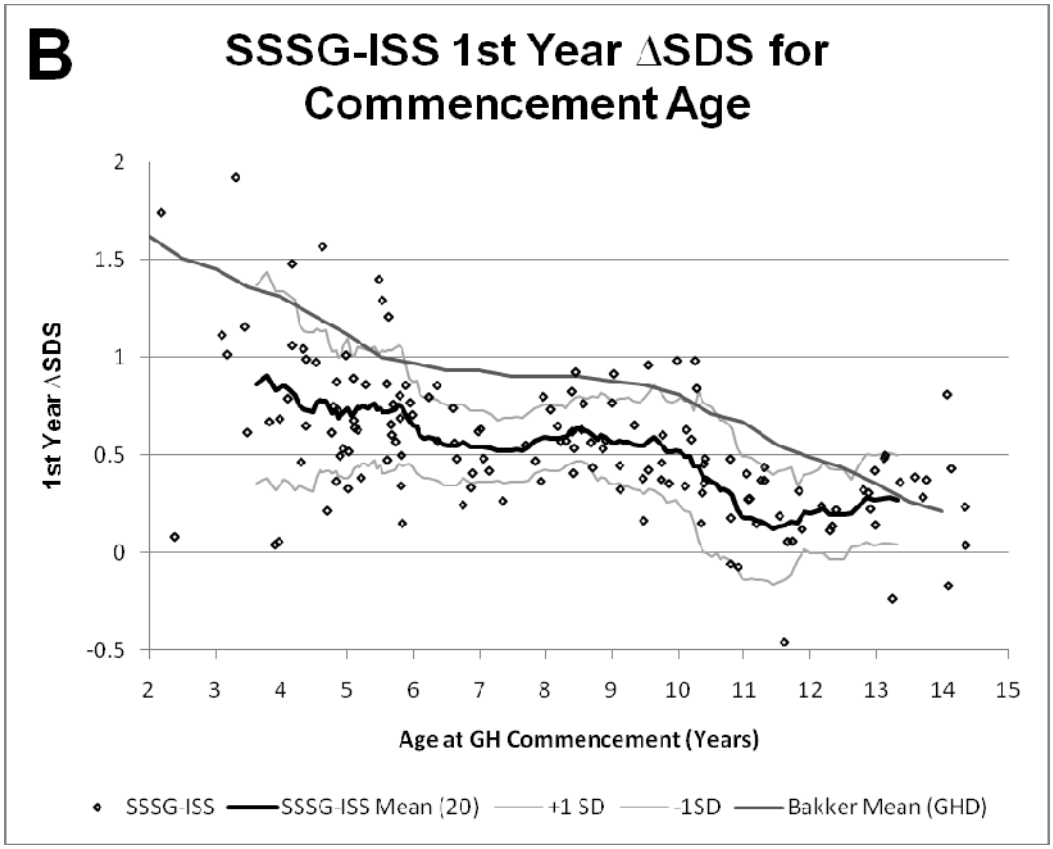


Figure 1. Height SDS for each year of GH treatment for the GHD indication and the ISS and FSS diagnoses within the SSSG indication.


A
BGHD 1st Year ΔSDS for Commencement Age
1st Year ΔSDS
3.5
3
2.5
2
1.5
1
0.5
0
-0.5
-1
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Age at GH Commencement (Years)
GHD Y1 dSDS
GHD Mean (20)
+1SD
-1SD
Bakker Mean
Female (20)
Male (20)


B
SSSG-ISS 1st Year ΔSDS for Commencement Age
1st Year ΔSDS
2
1.5
1
0.5
0
-0.5
2 3 4 5 6 7 8 9 10 11 12 13 14 15
Age at GH Commencement (Years)
SSSG-ISS
SSSG-ISS Mean (20)
+1 SD
-1SD
Bakker Mean (GHD)

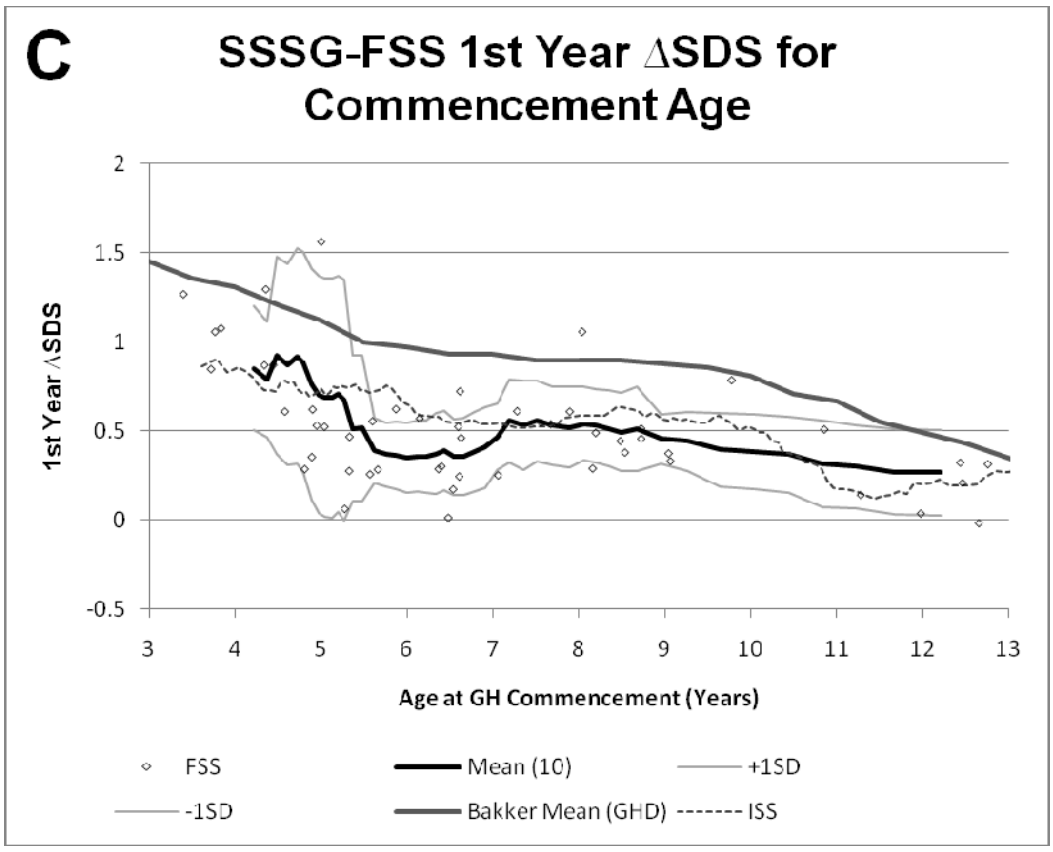

C
SSSG-FSS 1st Year ΔSDS for Commencement Age
1st Year ΔSDS
2
1.5
1
0.5
0
-0.5
3 4 5 6 7 8 9 10 11 12 13
Age at GH Commencement (Years)
FSS
Mean (10)
+1SD
-1SD
Bakker Mean (GHD)
ISS

Figure 2. First year response to GH treatment (ΔSDS). Moving Mean+/- SD (20 individuals) plotted against age at commencement of treatment. For comparison purposes the first year ΔSDS response for commencement age curve published by Bakker *et al.(13)* for boys with idiopathic GHD is also shown. Panel A) BGHD: Individual curves for males and females are shown as response was seen to be different at commencement ages less than 5 years. Panel B) SSSG-ISS. Panel C) SSSG-FSS: Due to fewer patients, moving mean uses 10 patients. For direct comparison the SSSG-ISS curve is superimposed.

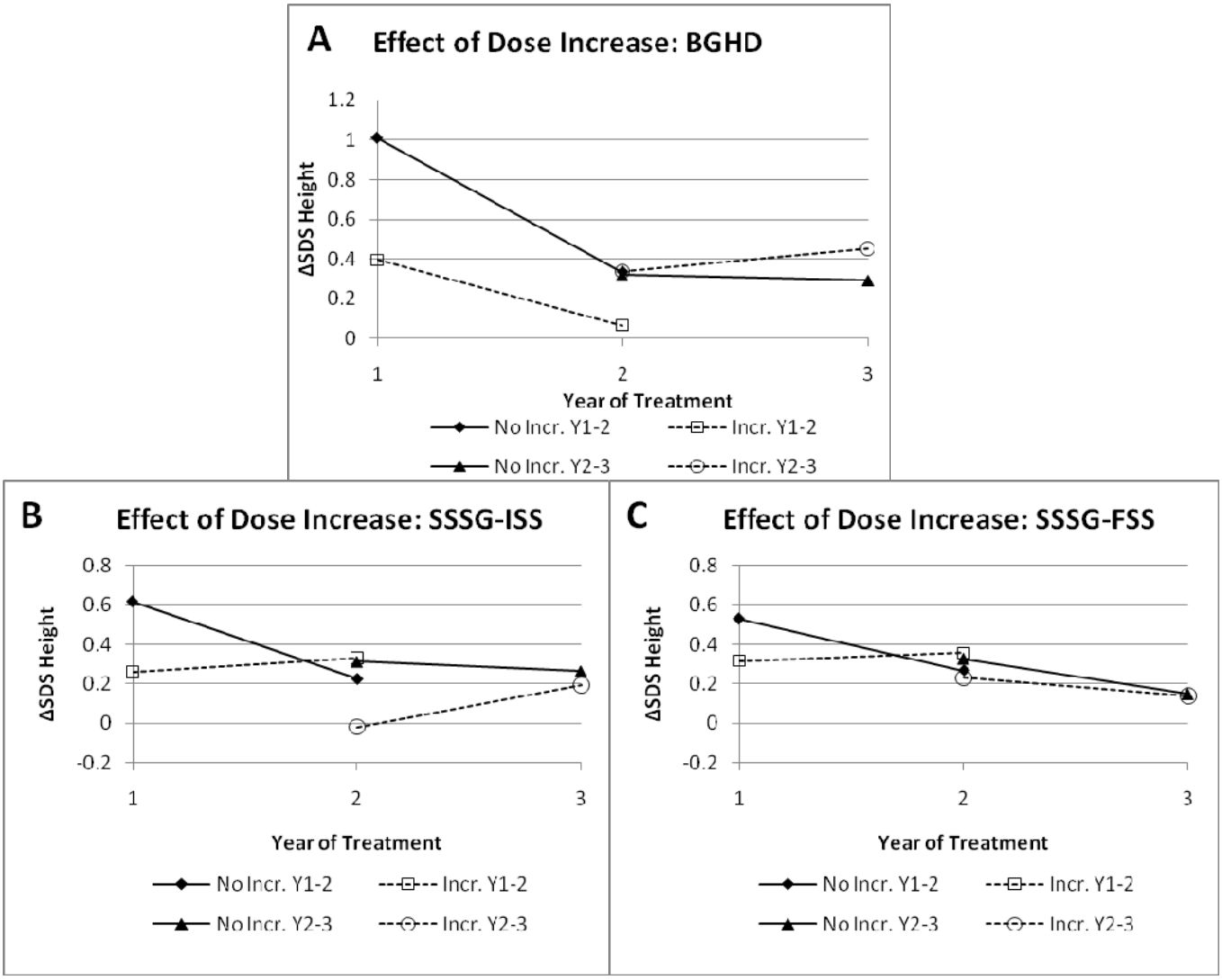
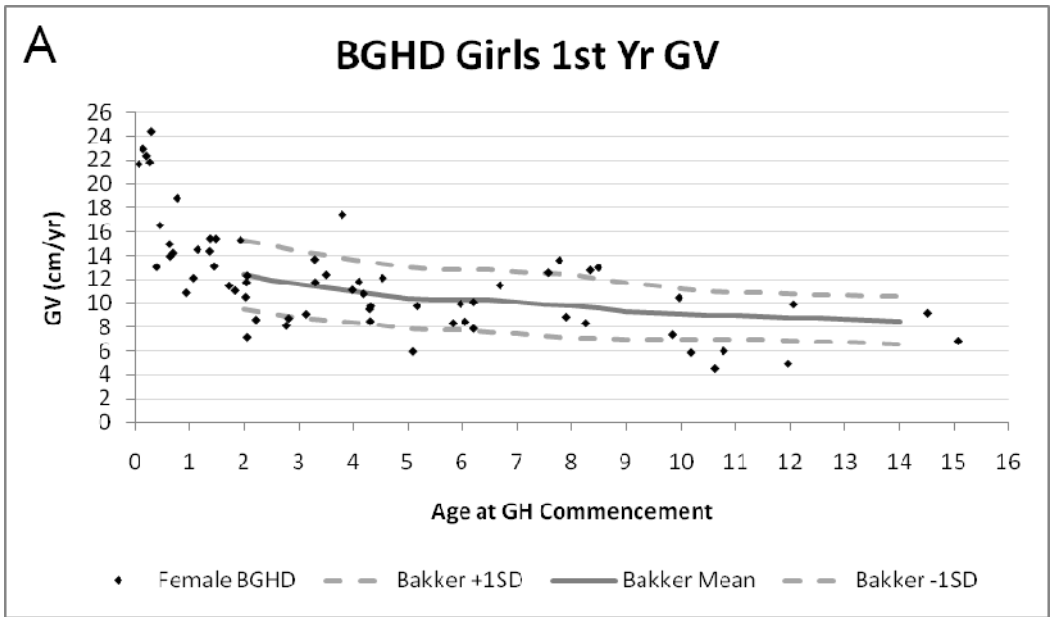
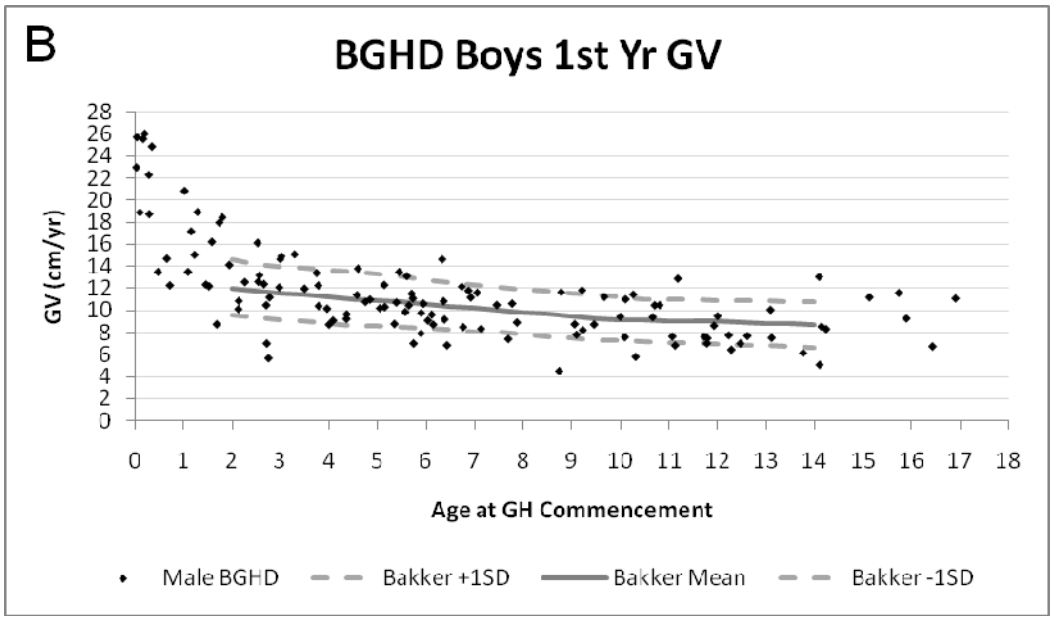


Figure 4. The effect of dose increment (annual mean dose increase >1mg/m^2/week) on response (ΔSDS Height) for increases from the 1st to 2nd years (Y1-2) of treatment and 2nd to 3rd years (Y2-3) of treatment for BGHD (Panel A), SSSG-ISS (Panel B), and SSSG-FSS (Panel C). Cohorts receiving a dose increase (dotted lines and open symbols) are compared to those who do not (solid lines and symbols).


A
BGHD Girls 1st Yr GV
GV (cm/yr)
Age at GH Commencement
Female BGHD
Bakker +1SD
Bakker Mean
Bakker -1SD


B
BGHD Boys 1st Yr GV
GV (cm/yr)
Age at GH Commencement
Male BGHD
Bakker +1SD
Bakker Mean
Bakker -1SD

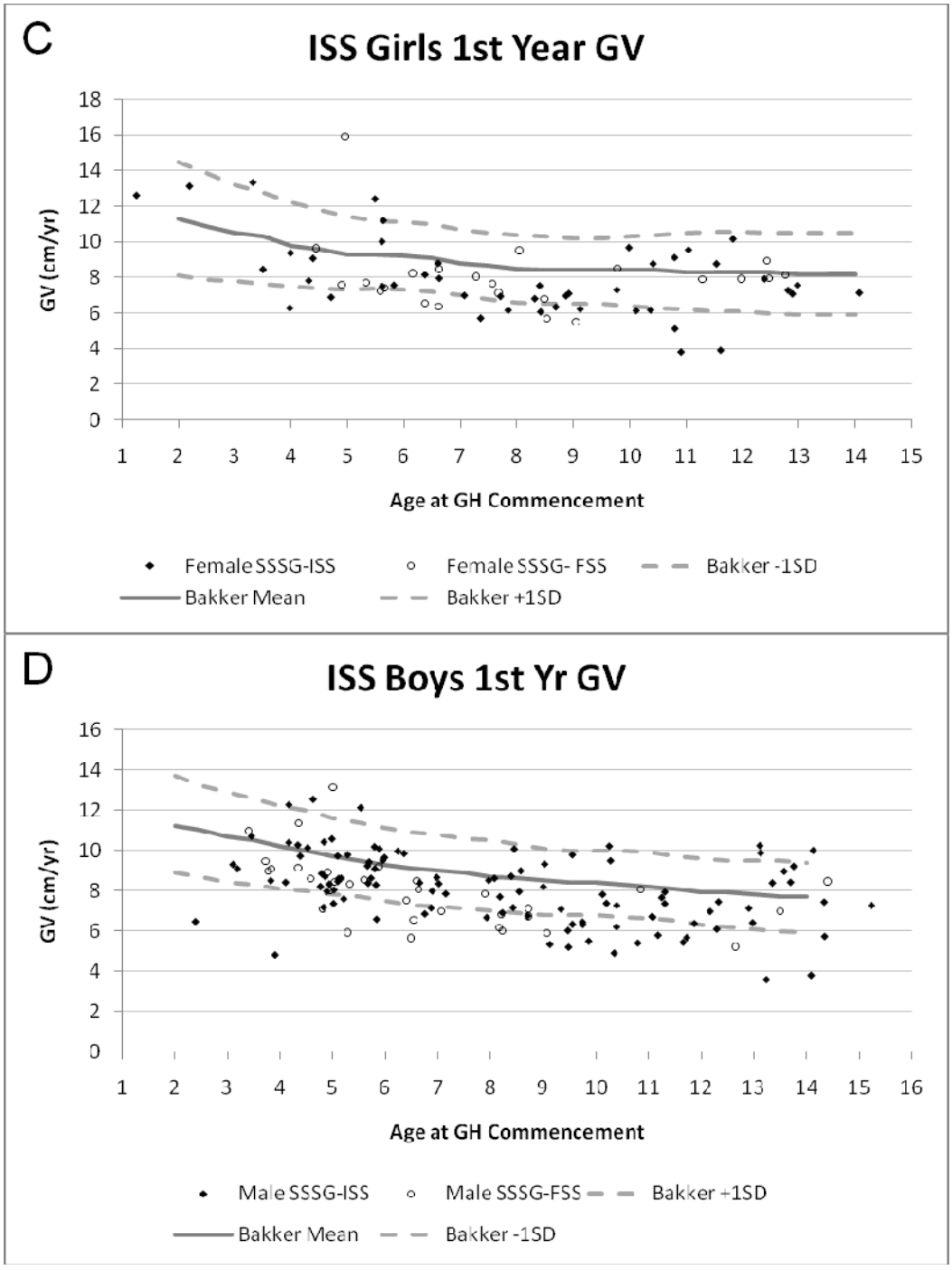


Figure 3. First year GV response compared to Bakker et al.(13) standards. Panel A: BGHD girls. Panel B: BGHD boys. Panel C: SSSG-ISS and SSSG-FSS girls. Panel D: SSSG-ISS and SSSG-FSS boys.

References

1. Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. J Clin Endocrinol Metab. 2008 Nov;93(11):4210-7.
2. Keni J, Cohen P. Optimizing growth hormone dosing in children with idiopathic short stature. Horm Res. 2009 Jan;71 Suppl 1:70-4.
3. Poyrazoglu S, Darendeliler F, Bas F, Bundak R, Saka N, Darcan S, et al. Target height estimation in children with idiopathic short stature who are referred to the growth clinic. Horm Res. 2009;72(3):178-83.
4. Ranke MB, Lindberg A, Price DA, Darendeliler F, Albertsson-Wikland K, Wilton P, et al. Age at growth hormone therapy start and first-year responsiveness to growth hormone are major determinants of height outcome in idiopathic short stature. Horm Res. 2007;68(2):53-62.
5. Roman R, Iniguez G, Lammoglia JJ, Avila A, Salazar T, Cassorla F. The IGF-I response to growth hormone is related to body mass index in short children with normal weight. Horm Res. 2009;72(1):10-4.
6. de Zegher F, Hokken-Koelega A. Growth hormone therapy for children born small for gestational age: height gain is less dose dependent over the long term than over the short term. Pediatrics. 2005 Apr;115(4):e458-62.
7. Garcia RA, Longui CA, Kochi C, Arruda M, Faria CD, Calliari LE, et al. First two years' response to growth hormone treatment in very young preterm small for gestational age children. Horm Res. 2009;72(5):275-80.
8. Australian-Government. Guidelines for the Availability of Human Growth Hormone (hGH) as a Pharmaceutical Benefit. 2007 [cited; Available from:
9. Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr. 1985 Sep;107(3):317-29.
10. Kristrom B, Dahlgren J, Niklasson A, Nierop AF, Albertsson-Wikland K. The first-year growth response to growth hormone treatment predicts the long-term prepubertal growth response in children. BMC Med Inform Decis Mak. 2009;9:1.
11. Reiter EO, Price DA, Wilton P, Albertsson-Wikland K, Ranke MB. Effect of growth hormone (GH) treatment on the near-final height of 1258 patients with idiopathic GH deficiency: analysis of a large international database. J Clin Endocrinol Metab. 2006 Jun;91(6):2047-54.
12. Rachmiel M, Rota V, Atenafu E, Daneman D, Hamilton J. Final height in children with idiopathic growth hormone deficiency treated with a fixed dose of recombinant growth hormone. Horm Res. 2007;68(5):236-43.
13. Bakker B, Frane J, Anhalt H, Lippe B, Rosenfeld RG. Height velocity targets from the national cooperative growth study for first-year growth hormone responses in short children. J Clin Endocrinol Metab. 2008 Feb;93(2):352-7.
14. Wit JM, Rekers-Mombarg LT, Cutler GB, Crowe B, Beck TJ, Roberts K, et al. Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. J Pediatr. 2005 Jan;146(1):45-53.
15. Wit JM, Rekers-Mombarg LT. Final height gain by GH therapy in children with idiopathic short stature is dose dependent. J Clin Endocrinol Metab. 2002 Feb;87(2):604-11.

16. Wit JM, Reiter EO, Ross JL, Saenger PH, Savage MO, Rogol AD, et al. Idiopathic short stature: management and growth hormone treatment. Growth Horm IGF Res. 2008 Apr;18(2):111-35.
17. Cowell CT, Dietsch S, Greenacre P. Growth hormone therapy for 3 years: the OZGROW experience. J Paediatr Child Health. 1996 Apr;32(2):86-93.
18. Werther GA, Wang M, Cowell CT. An auxology-based growth hormone program: update on the Australian experience. J Pediatr Endocrinol Metab. 2003 May;16 Suppl 3:613-8.
19. NHANES. CDC Growth Charts: United States. U.S. Department of Health and Human Services; 2008.
20. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med. 1987 Oct 22;317(17):1098.
21. Greulich W, Pyle S. Radiographic Atlas of Skeletal Development of the Hand and Wrist, ed 2. . Stanford: Stanford University Press; 1959.
22. Cole TJ, Hindmarsh PC, Dunger DB. Growth hormone (GH) provocation tests and the response to GH treatment in GH deficiency. Arch Dis Child. 2004 Nov;89(11):1024-7.
23. de Ridder MA, Stijnen T, Hokken-Koelega AC. Prediction of adult height in growth-hormone-treated children with growth hormone deficiency. J Clin Endocrinol Metab. 2007 Mar;92(3):925-31.
24. Dahlgren J, Kristrom B, Niklasson A, Nierop AF, Rosberg S, Albertsson-Wikland K. Models predicting the growth response to growth hormone treatment in short children independent of GH status, birth size and gestational age. BMC Med Inform Decis Mak. 2007;7:40.
25. Cohen P, Bright GM, Rogol AD, Kappelgaard AM, Rosenfeld RG. Effects of dose and gender on the growth and growth factor response to GH in GH-deficient children: implications for efficacy and safety. J Clin Endocrinol Metab. 2002 Jan;87(1):90-8.
26. Ranke MB, Lindberg A. Observed and predicted growth responses in prepubertal children with growth disorders: guidance of growth hormone treatment by empirical variables. J Clin Endocrinol Metab. 2010 Mar;95(3):1229-37.
27. Cutfield WS, Lundgren F. 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. Horm Res. 2009 Jan;71 Suppl 1:39-45.
28. Ranke MB, Lindberg A, Albertsson-Wikland K, Wilton P, Price DA, Reiter EO. Increased response, but lower responsiveness, to growth hormone (GH) in very young children (aged 0-3 years) with idiopathic GH Deficiency: analysis of data from KIGS. J Clin Endocrinol Metab. 2005 Apr;90(4):1966-71.
29. Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield W, Albertsson-Wikland K, et al. Derivation and validation of a mathematical model for predicting the response to exogenous recombinant human growth hormone (GH) in prepubertal children with idiopathic GH deficiency. KIGS International Board. Kabi Pharmacia International Growth Study. J Clin Endocrinol Metab. 1999 Apr;84(4):1174-83.
30. Ranke MB, Lindberg A, Martin DD, Bakker B, Wilton P, Albertsson-Wikland K, et al. The mathematical model for total pubertal growth in idiopathic growth hormone (GH) deficiency suggests a moderate role of GH dose. J Clin Endocrinol Metab. 2003 Oct;88(10):4748-53.
31. Wit JM. 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). Horm Res. 2007;68(5):244-7.
32. Sudfeld H, Kiese K, Heinecke A, Bramswig JH. Prediction of growth response in prepubertal children treated with growth hormone for idiopathic growth hormone deficiency. Acta Paediatr. 2000 Jan;89(1):34-7.
33. Bang P, Bjerknes R, Dahlgren J, Dunkel L, Gustafsson J, Juul A, et al. A Comparison of Different Definitions of Growth Response in Short Prepubertal Children Treated with Growth Hormone. Horm Res Paediatr. Jan 12.
34. Geffner ME, Dunger DB. Future directions: growth prediction models. Horm Res. 2007;68 Suppl 5:51-6.
35. Westphal O, Lindberg A. Final height in Swedish children with idiopathic growth hormone deficiency enrolled in KIGS treated optimally with growth hormone. Acta Paediatr. 2008 Dec;97(12):1698-706.
36. Albertsson-Wikland K, Aronson AS, Gustafsson J, Hagenas L, Ivarsson SA, Jonsson B, et al. Dose-dependent effect of growth hormone on final height in children with short stature without growth hormone deficiency. J Clin Endocrinol Metab. 2008 Nov;93(11):4342-50.
37. Thangavel C, Shapiro BH. A molecular basis for the sexually dimorphic response to growth hormone. Endocrinology. 2007 Jun;148(6):2894-903.
38. Rose SR, Shulman DI, Larsson P, Wakley LR, Wills S, Bakker B. Gender does not influence prepubertal growth velocity during standard growth hormone therapy--analysis of United States KIGS data. J Pediatr Endocrinol Metab. 2005 Nov;18(11):1045-51.
39. van Pareren YK, de Muinck Keizer-Schrama SM, Stijnen T, Sas TC, Jansen M, Otten BJ, et al. Final height in girls with turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. J Clin Endocrinol Metab. 2003 Mar;88(3):1119-25.
40. Sas TC, de Ridder MA, Wit JM, Rotteveel J, Oostdijk W, Reeser HM, et al. Adult height in children with growth hormone deficiency: a randomized, controlled, growth hormone dose-response trial. Horm Res Paediatr.74(3):172-81.
41. Wilson TA, Rose SR, Cohen P, Rogol AD, Backeljauw P, Brown R, et al. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr. 2003 Oct;143(4):415-21.
42. Cohen P, Germak J, Rogol AD, Weng W, Kappelgaard AM, Rosenfeld RG. Variable Degree of Growth Hormone (GH) and Insulin-Like Growth Factor (IGF) Sensitivity in Children with Idiopathic Short Stature Compared with GH-Deficient Patients: Evidence from an IGF-Based Dosing Study of Short Children. J Clin Endocrinol Metab. Mar 5.