A randomised controlled trial evaluating IGF1 titration in contrast to current GH dosing strategies in children born small for gestational age: the North European Small-for-Gestational-Age Study

Rikke Beck Jensen[1,2], Ajay Thankamony[2], Susan M O'Connell[3], Jeremy Kirk[4], Malcolm Donaldson[5], Sten-A Ivarsson[6], Olle Söder[7], Edna Roche[3], Hilary Hoey[3], David B Dunger[2] and Anders Juul[1]

[1]Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2]Department of Pediatrics, Addenbrooke's Hospital, University of Cambridge, Hills Road, CB2 0QQ Cambridge, UK, [3]Department of Pediatrics, The National Children's Hospital, Trinity College, University of Dublin, Dublin, Ireland, [4]Department of Endocrinology, Birmingham Children's Hospital, Birmingham, UK, [5]Department of Endocrinology, Royal Hospital for Sick Children, Glasgow, UK, [6]Department of Clinical Sciences, Endocrine and Diabetes Unit, University of Lund, Malmø, Sweden and [7]Pediatric Endocrinology Unit, Department of Women's and Children's Health, Karolinska Institutet and University Hospital, Stockholm, Sweden

Correspondence
should be addressed
to R B Jensen
Email
rikke.beck@dadlnet.dk

Abstract

Background: Short children born small for gestational age (SGA) are treated with a GH dose based on body size, but treatment may lead to high levels of IGF1. The objective was to evaluate IGF1 titration of GH dose in contrast to current dosing strategies.

Methods: In the North European Small-for-Gestational-Age Study (NESGAS), 92 short pre-pubertal children born SGA were randomised after 1 year of high-dose GH treatment (67 μg/kg per day) to three different regimens: high dose (67 μg/kg per day), low dose (35 μg/kg per day) or IGF1 titration.

Results: The average dose during the second year of the randomised trial did not differ between the IGF1 titration group (38 μg/kg per day, s.d. 0.019) and the low-dose group (35 μg/kg per day, s.d. 0.002; $P=0.46$), but there was a wide variation in the IGF1 titration group (range 10–80 μg/kg per day). The IGF1 titration group had significantly lower height gain (0.17 SDS, s.d. 0.18) during the second year of the randomised trial compared with the high-dose group (0.46 SDS, s.d. 0.25), but not significantly lower than the low-dose group (0.23 SDS, s.d. 0.15; $P=0.17$). The IGF1 titration group had lower IGF1 levels after 2 years of the trial (mean 1.16, s.d. 1.24) compared with both the low-dose (mean 1.76, s.d. 1.48) and the high-dose (mean 2.97, s.d. 1.63) groups.

Conclusion: IGF1 titration of GH dose in SGA children proved less effective than current dosing strategies. IGF1 titration resulted in physiological IGF1 levels with a wide range of GH dose and a poorer growth response, which indicates the role of IGF1 resistance and highlights the heterogeneity of short SGA children.

Introduction

Small for gestational age (SGA) is a heterogeneous condition, which is a result of impaired foetal growth caused by multifactorial environmental factors *in utero* or as yet unidentified genetic disorders. Among the 10% of

the SGA children who do not catch up during infancy, some have low insulin-like growth factor 1 (IGF1) levels suggesting alterations of the growth hormone (GH)/IGF1 axis (1, 2). However, the majority of short SGA children have sufficient GH secretion and some children have IGF1 levels above mean, which has been linked to a relative IGF1 resistance in some of the patients.

Randomised controlled trials have documented the beneficial effects of GH therapy on both short- and long-term growth in short children born SGA (3, 4, 5), and this indication for GH treatment was approved in 2001 in USA and in 2003 in Europe (6). However, the current recommended doses of GH used for short SGA children vary widely from 70 μg/kg per day in the US to 35 μg/kg per day in Europe, and the optimal GH dose regimen for children born SGA continues to be a matter of debate (7). Treatment with a higher dose of GH leads to an improved short-term growth response and a faster normalisation of height (8, 9), which we have recently confirmed in the North European Small-for-Gestational-Age Study (NESGAS) (10). While lower doses of GH may be equally effective in the long term, catch-up growth is less dramatic and may be variable, with some children requiring higher doses in the second year of treatment (8, 11, 12, 13, 14). Concern has been raised because both high doses as used in the USA and lower doses used in Europe can lead to unacceptably high levels of IGF1, which may have unknown long-term consequences. The basis of this concern relates to the finding of modest associations between higher circulating IGF1 and IGFBP3 levels and an increased risk of developing common cancers (15); however, this has not been evaluated in relation to SGA.

An alternative strategy to the conventional GH dosing regimen based on body size is dosing by IGF1 levels, which offers the opportunity to potentially tailor the GH dose to retain efficacy without exposing the subjects to high IGF1 levels. Experience in GH-deficient (GHD) and idiopathic short-stature (ISS) children demonstrated not only an increased growth response, but also a higher average GH dose, in those with GH titrated to the upper limit of normal IGF1 (SDS) levels compared with those titrated to achieve a mean IGF1 (SDS) or the conventional dose (16, 17, 18). IGF1 titration of GH doses in SGA children has not been explored previously.

In this study, after 1 year of high-dose GH treatment, the NESGAS patients were randomised to three groups: i) high-dose (67 μg/kg per day) GH, ii) low-dose (35 μg/kg per day) GH or iii) IGF1 titrated dose in order to explore the potential of IGF1 titration of GH dose in a well-characterised group of SGA children.

Patients and methods

Study population

NESGAS is a multicentre, randomised, parallel group study of GH treatment in short pre-pubertal children born SGA. Study design and first year data have been reported in detail previously (10). In brief, all children were treated with a uniform high dose (67 μg/kg per day) of GH for the first year of treatment in order to induce catch-up growth. All patients who had completed 1 year of high-dose (67 μg/kg per day) GH treatment had a height velocity of more than 1 SDS (ΔHVSDS > +1) and were randomised into one of the three groups (Fig. 1). The study (NESGAS EudraCT 2005-001507-19) was approved by the ethics committee or institutional review board and national drug authorities at each study centre and was performed according to the Helsinki II declaration. Written informed consent was obtained from guardians of each child before recruitment.

Intervention

The cohort was randomly assigned to three different dose regimens for 2 years (ratio 1:1:1). Allocation of patients was performed through minimisation (MINIM, Sealed Envelope, sealedenvelope.com) (19) to ensure equal distribution between study groups. Minimisation related to:

i) First-year growth response: HVSDS ≥ +2.5 (good responder) or HVSDS between +1 and +2.5 (medium responder).
ii) Gender.
iii) Age (4–6 years/6–9 years).
iv) Country.

Patients were randomised to one of the three dosing regimens of recombinant human GH (Norditropin, Novo Nordisk, Bagsvaerd, Denmark) given as a daily s.c. injection. The regimens included the high-dose regimen (67 μg/kg per day), low-dose regimen (35 μg/kg per day) and IGF1 titration regimen.

IGF1 titration of the GH dose

In the IGF1 titration group, the GH dose was adjusted every three months according to the IGF1 levels measured at each quarterly visit using an algorithm to maintain IGF1 SDS levels between 0 and +2 SDS (Supplementary Figure 1, see section on supplementary data given at the end of this article).
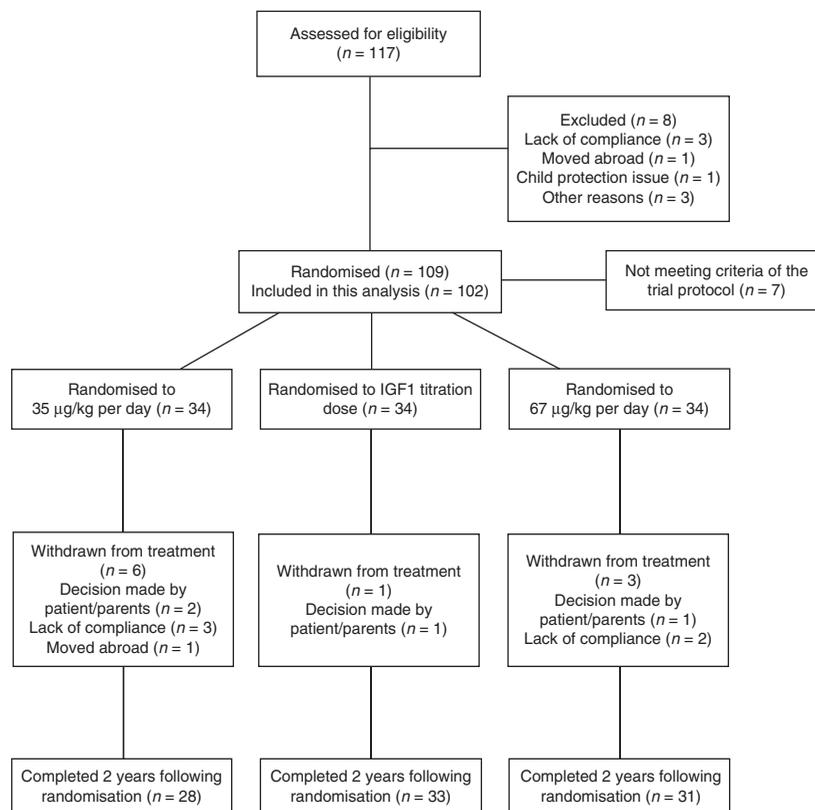
Figure 1

Flow diagram of the process through the phases of the parallel randomised trial.

Outcome measure

The primary outcome measure was the height gain (ΔHtSDS) during the second year of the trial. The secondary endpoints were changes in IGF1 levels (ΔIGF1) and changes in bone age (ΔBA).

Study assessments

Participants were assessed at study entry and at every 3 months, where the following were measured: standing height on a wall-mounted stadiometer and weight by electronic scales by staff trained in auxological methods. At each visit, pubertal development was assessed by an experienced investigator. Bone age was determined ad modum Greulich–Pyle.

Laboratory measurements

Serum IGF1 and IGFBP3 concentrations were determined centrally in Copenhagen using a solid-phase enzyme-labelled chemiluminescent immunometric assay

(Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA). Standards were calibrated towards the WHO NIBSC IRR 87/518. Detection limit for IGF1 was 20 ng/ml, and inter- and intra-assay coefficient of variation (CV) values were 5.93 and 2.02% respectively. The detection limit for IGFBP3 was 500 ng/ml, and inter- and intra-assay CV values were 5.23 and 1.74% respectively. IGF1 and IGFBP3 SDS were calculated from our reference data (20).

Calculations

SDS were derived for birth weight, birth length, height, weight, BMI, IGF1 and IGFBP3 using central country-specific reference databases (21, 22, 23). Target height SDS was computed using the formula (maternal HtSDS + paternal HtSDS)/2. For some of the analysis, the cohort was divided into tertiles according to the IGF1 levels before the start of treatment (IGF1 baseline). ΔBA was calculated: $BA_{2yr} - BA_{before\ randomisation}$. BA corrected for chronological age (CA) was calculated as $BA - CA$.

Statistical analyses

The variables were analysed for normal distribution using the Kolmogorov–Smirnov test and were transformed to normality if necessary. Differences between groups were analysed using ANOVA or Student's t test where appropriate. The Pearson χ^2-test was performed to compare pubertal development between the groups. Statistical analyses were performed using the statistical package IBM SPSS statistics (version 21; SPSS, Inc.). Data are expressed as mean (s.d.) or back-transformed geometric mean (1 s.d. range) unless otherwise specified.

Based on power calculations for the primary outcome measure and assuming a 10% drop-out rate, recruitment of 112 patients was required to detect 0.25 s.d. increases in height SDS with 80% statistical power at a 5% significance level using a two-sided t-test.

Safety parameters

Safety assessments were carried out at each visit and recorded on a standard adverse event form. For serious adverse events (SAEs), serious adverse reactions (SARs) and suspected unexpected SARs (SUSARs), a form was completed and reported to the chief investigator. Adverse events were reported to the Health Authorities and Independent Review Boards/Independent Ethics Committees in accordance with national laws and regulations.

Results

Clinical characteristics

Longitudinal data were included from the 92 participants (61 males) who completed the 2 years of the randomised trial (Fig. 1). Clinical characteristics did not differ among the three groups at randomisation (Table 1).

Two-year randomised trial

As expected, the regimen of high-dose GH therapy for 2 years resulted in greater height gain (ANOVA $P<0.0001$) and weight gain (ANOVA $P=0.002$) during the last year of the trial compared with both the low-dose and IGF1 titration groups (Table 2). In the IGF1 titration group there was a trend towards a lower growth response (0.15, s.d. 0.16) during the last year of the trial when compared with the low-dose group (0.24, s.d. 0.18), although this was not significant ($P=0.17$; Fig. 2a).

The average GH dose in the IGF1 titration group during the first year of the randomised trial was significantly higher than that in the low-dose group (mean 49.2 µg/kg per day, s.d. 13.8 vs mean 35 µg/kg per day, s.d. 1.60, $P<0.0001$), whereas the average dose during the second year of the randomised trial did not differ between the IGF1 titration group (mean 38 µg/kg per day, s.d. 18.86) and the low-dose group (mean 35 µg/kg per day,

Table 1 Clinical characteristics at birth, before start of GH treatment and before randomisation. Results are expressed as mean (s.d.). Comparison was performed by ANOVA. If significance was reached, an additional comparison was performed by Student's t test between the low dose and the IGF1 titrated dose.

| | GH dosing regimens | | | |
	Low dose	IGF1 titration dose	High dose	*P* values
n (Boys)	28 (17)	33 (21)	31 (23)	
Birth				
Birth weight (SDS)	−3.52 (1.12)	−3.64 (1.29)	−3.88 (1.33)	0.53
Birth length (SDS)	−3.34 (1.17)	−4.20 (2.06)	−3.38 (1.55)	0.17
Gestational age (week)	36.09 (3.69)	34.76 (4.54)	35.86 (3.51)	0.38
Target height (SDS)	−1.23 (1.19)	−1.25 (1.06)	−1.06 (1.02)	0.75
Before start of GH				
Age (year)	6.29 (1.59)	5.93 (1.60)	6.32 (1.68)	0.57
Height (SDS)	−3.47 (0.73)	−3.50 (0.87)	−3.27 (0.57)	0.41
Weight (SDS)	−3.14 (0.94)	−3.30 (1.03)	−3.18 (1.00)	0.80
BMI (SDS)	−1.22 (1.36)	−1.25 (1.23)	−1.42 (1.32)	0.82
IGF1 (SDS)	−1.12 (1.02)	−1.31 (1.11)	−0.86 (1.22)	0.26
IGFBP3 (SDS)	−1.05 (1.05)	−0.74 (1.13)	−0.57 (1.07)	0.30
Before randomisation				
Height (SDS)	−2.39 (0.82)	−2.47 (0.82)	−2.27 (0.70)	0.59
Weight (SDS)	−1.99 (0.98)	−2.37 (0.91)	−2.12 (1.03)	0.31
BMI (SDS)	−0.72 (1.23)	−1.13 (0.99)	−1.12 (1.32)	0.31
IGF1 (SDS)	2.57 (1.26)	2.84 (1.77)	2.69 (1.24)	0.77
IGFBP3 (SDS)	1.07 (0.74)	1.16 (1.23)	1.49 (0.81)	0.22

Table 2 Effects of the three different dosing regimens on growth after 2 years of the trial. Results are expressed as mean (s.d.). Delta values show the change of the variables from before randomisation to the end of randomisation. Comparison was performed by ANOVA. If significance was reached, an additional comparison was performed by Students t test between the low dose and the IGF1 titrated dose. Statistical significance is marked with *.

	GH dosing regimens			
	Low dose (35 µg/kg per day)	IGF1 titration dose	High dose (67 µg/kg per day)	**P values**
At the end of 2 years of randomisation				
n (Boys)	28 (17)	33 (21)	30 (23)	
Age (years)	9.33 (1.61)	9.07 (1.61)	9.38 (1.60)	0.73
Height (SDS)	−1.76 (0.94)	−1.95 (0.85)	−1.24 (0.91)	**0.008**
Weight (SDS)	−1.31 (1.02)	−1.70 (0.90)	−1.08 (1.04)	**0.045**
BMI (SDS)	−0.48 (1.35)	−1.04 (1.34)	−0.60 (1.30)	0.23
IGF1 (SDS)	1.76 (1.48)	1.16 (1.24)	3.04 (1.60)	**<0.0001**
IGFBP3 (SDS)	1.23 (1.09)	0.73 (1.17)	1.88 (0.86)	**0.001**
Pubic Hair (I, II, III)[a]	26/0/0	26/3/0	22/4/0	0.13
Breast (I/II/III)[a]	7/2/0	11/1/0	6/1/0	0.70
Change during the last year of randomisation				
ΔHeight (SDS)	0.23 (0.15)	0.17 (0.18)	0.46 (0.23)	**<0.0001**
ΔWeight (SDS)	0.27 (0.27)	0.16 (0.24)	0.42 (0.30)	**0.002**
ΔBMI (SDS)	0.13 (0.35)	−0.15 (0.86)	0.19 (0.39)	0.08
ΔIGF1 (SDS)	0.03 (1.14)	−0.69 (0.89)*	0.10 (1.21)	**0.02**
ΔIGFBP3	0.69 (1.18)	−0.07 (1.10)*	0.59 (0.27)	**0.04**

[a]The Pearson χ^2 test was used for comparison of pubertal development between groups.

s.d. 1.76) ($P=0.30$). Noticeably, there was a wide variation of the GH dose in the IGF1 titration group ranging from 10 to 80 µg/kg per day and also wide differences in growth response to GH therapy (Fig. 3). In the IGF1 titration group, 22 subjects (66%) achieved changes in HtSDS comparable to the low-dose group (ΔHtSDS 0.24±0.18; Fig. 4). In these subjects, this was achieved with a GH dose of 37 µg/kg per day (s.d. 17.00) and IGF1 levels of 1.53 (s.d. 0.86). In the remaining 11 subjects, gains in HtSDS (−0.03, s.d. 0.07) were lower than those observed in the low-dose group. Eight of these patients had IGF1 levels in the highest tertile at the start of GH treatment and their persistently higher IGF1 levels led to down-titration of GH doses to below 20 µg/kg per day (Fig. 4). This group had a significantly lower growth response during the second year of treatment compared with the subjects in the middle or low tertiles of baseline IGF1 levels (data not shown). By contrast, one patient had a poor growth response (ΔHtSDS −0.17) despite a GH dose of 60 µg/kg per day during the second year of the randomised trial. This patient had very low IGF1 levels at baseline (−3.21 s.d.) and the poor growth response may have been due to poor adherence. Overall comparisons between the three dosing regimens during the 2 years of the trial are shown in Table 2.

There were no significant differences among the low-dose, high-dose or IGF1 titration groups for changes either in bone age during the 2 years of the trial (ANOVA $P=0.38$) or bone age corrected for CA after 2 years of treatment (ANOVA $P=0.27$).

IGF1 levels

IGF1 levels were lower in the IGF1 titration group after 2 years of the trial (mean 1.16, s.d. 1.24) compared with the low-dose (mean 1.76, s.d. 1.48) and the high-dose (mean 2.97, s.d. 1.63) groups (Table 2 and Fig. 2b). IGF1 titration was associated with decreasing IGF1 levels during the first year of the trial, and IGF1 levels were titrated to levels between 0 and +2.5 SDS in 75% of patients ($n=24$) after 1 year of the trial. All of the patients in the IGF1 titration group had IGF1 (SDS) levels below +2.5 SDS after 2 years of the trial (Fig. 2) compared with only 64% ($n=16$) in the low-dose group and 40% ($n=8$) in the high-dose group. Some patients had continuously elevated IGF1 SDS levels up to +4.55 SDS and +5.63 SDS in the low-dose and high-dose groups respectively (Fig. 2).

Safety

During the 2 years of randomisation, eight SAEs were reported, but no SARs or SUSARs. There was no difference between the three groups of randomisation in reporting of
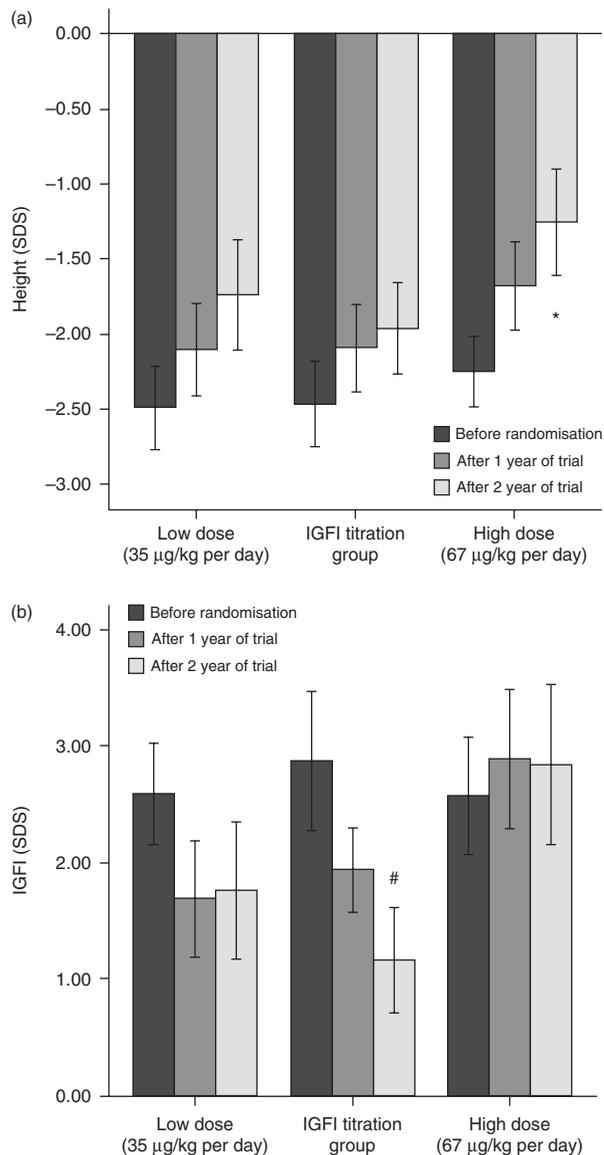
Figure 2

(a) Mean height (SDS) ± 2 s.e. at 12 months (black bars), 24 months (dark grey bars) and 36 months (light grey) of GH treatment in the three groups of randomisation: low-dose (35 μg/kg per day) group, IGF1 titration group and high-dose (67 μg/kg per day) group. (b) Mean IGF1 (SDS) ± 2 s.e. at 12 months (black bars), 24 months (dark grey bars) and 36 months (light grey) of GH treatment in the three groups of randomisation: low-dose (35 μg/kg per day) group, IGF1 titration group and high-dose (67 μg/kg per day) group.

SAEs: two SAEs in the low-dose group (one diagnosed with asthma, one with hypertrophy of the adenoids and adenoidectomy), three SAEs in the high-dose group (one with fracture of the radius after falling, one with torticollis and one girl, with cerebral palsy, who was diagnosed with epilepsy) and three SAEs in the IGF1 titration group (one developed scoliosis and was diagnosed with juvenile idiopathic arthritis, one had viral meningitis and one patient had a reoperation of hypospadias).

Discussion

In this randomised trial, growth response to the two established GH doses was, as expected, accompanied by high IGF1 levels, but the ability of the IGF1 titrated dose to mitigate these exposures was more variable. Personalising GH therapy in SGA to avoid high IGF1 exposures is attractive; however, this study emphasises that titration of GH dose from IGF1 levels alone may not result in the optimal growth response in short SGA children.

SGA is a heterogeneous condition and impaired postnatal growth in this group of patients may arise from a variety of effects on the GH/IGF1 axis including GH and IGF1 resistance. Variation in the responsiveness to GH therapy implies that individualised dosing of GH according to GH sensitivity may be required in SGA patients. Cohen et al. (16, 17) showed that targeting higher IGF1 levels by increasing the GH dose in GHD and ISS children resulted in increased change in height in the group of patients who had a GH dosage titrated to achieve IGF1 levels in the upper limit of the normal range compared with those who either had the fixed conventional dose or had received a dosage titrated to achieve IGF1 levels at the mean of a normal range. However, this study only included patients with low IGF1 levels (below −1 SDS), which may exclude those with potential IGF1 resistance. The algorithm used to titrate the GH dose in our study was different to that used in GHD and ISS patients. Mean IGF1 level after the first year of the randomised trial was +1.94 SDS (1.00 s.d.), whereas mean IGF1 level after 2 years of the trial was +1.16 SDS (1.24 s.d.) in the IGF1 titration group. This demonstrated that the algorithm worked in terms of achieving IGF1 levels between 0 and +2 SDS, but the lowering of GH dose according to IGF1 levels was prolonged as the algorithm only allowed a 15 μg/kg per day reduction in GH dose every 3 months. By contrast, the study on IGF1 titration in GHD and ISS children calculated the difference between measured and target IGF1 SDS using a 20% change in dose for each s.d. unit difference (16, 17, 18).

These data reflect the heterogeneity of SGA children. We and others have previously shown that SGA children with high baseline IGF1 levels show a poor response to GH therapy, a decreased IGF1 response and a lower
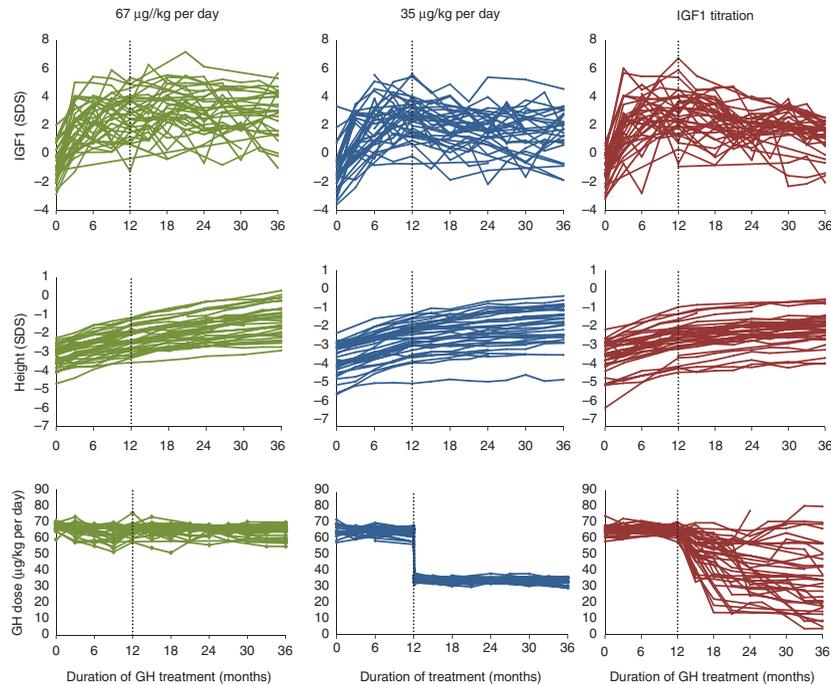
Figure 3

Individual longitudinal measurements of IGF1 (top row), height (middle row) and GH (bottom row) during 3 years of GH treatment in short SGA children according to three groups of randomisation: high dose (green), low dose (blue) and IGF1 titration (red).

insulin sensitivity (24, 25, 26), which indicates that some children have impaired hepatic IGF1 generation and potentially peripheral IGF1 resistance. Impairments in GH signalling pathways for hepatic IGF1 generation and down-regulation of peripheral IGF1 receptor have been demonstrated in experimental intrauterine growth retardation animal models (27, 28). As expected, we determined that, within the IGF1 titration group, eight out of ten patients with high baseline IGF1 levels had a poor growth during the second year of the randomised trial due to reductions in GH doses in response to persistently high IGF1 levels. Conversely, those with low IGF1 levels before the start of treatment were those with the best response, except one patient who responded poorly to a relatively high dose, where we suspected poor treatment adherence. Thus, IGF1 titration was underlining the importance of IGF1 resistance in this group of patients, indicating that some of these patients probably will need continuously maintained supra-physiological IGF1 levels in order to increase growth. The heterogeneity of the group of short SGA children calls for individualised GH therapy. Further studies may identify better predictors of GH response in order to enable a

Figure 4

Box plots reflecting change in height (SDS) during the second year of the randomised trial in the low-dose and high-dose groups. The dots show the individual change in height per GH dose in the IGF1 titration group according to baseline IGF1 levels (red: highest tertile, blue: middle tertile, green: lowest tertile).

more accurate personalised medicine approach including IGF1 levels, growth response and other possible biomarkers. However, from our study, IGF1 titration of the GH dose alone cannot be recommended in this population routinely, as it may lead to sub-optimal growth in some subjects.

One of the strengths of this study is the design, where all patients were treated with a uniform high dose of GH during the first year of therapy in order to induce catch-up growth. This was based on the knowledge that first-year growth response to GH treatment in SGA children is highly dose dependent, whereas the dose–response effect tends to level out during the following years of treatment (12). Thus, this study was designed to reduce the dose-dependent variation of growth response during the following years of treatment where the three different dosing regimens were explored.

There is an ongoing discussion about the long-term safety of GH treatment in relation to the development of cardiovascular and metabolic disorders and malignancies, but the results are inconsistent (29, 30). In adult populations, increased circulating concentrations of IGF1 have retrospectively been found to be related to an increased risk of development of cancer, but this relationship is not universally observed (15). Though, during puberty, the growth spurt is associated with exposure to high physiological levels of IGF1. In this study, we found no safety issues in the short term. Although high IGF1 levels could be a risk factor for later disease, this may not be true in a population such as those born SGA, where some of the patients will be IGF1 resistant and thereby require higher IGF1 levels to improve growth. On the other hand, although the short-term growth response in the IGF1 titration group was lower than the low-dose group, this may reflect a more physiological response to GH, which could be speculated to have beneficial effects on the long-term consequences of the treatment.

This randomised trial is the first to demonstrate the effects of an individualised dosing regimen by titration of the GH dose according to the IGF1 levels in short children born SGA. Theoretically, dosing based on IGF1 levels may not only mimic a more physiological growth response and potentially lower the long-term risk for adverse effects of the treatment, but may also be valuable from a cost–benefit point of view (31). However, our data of dose titration in SGA children proved to be less effective especially in those patients who had a degree of IGF1 resistance, as they are dependent on continuous supra-physiological IGF1 levels in order to grow.

Although we cannot recommend IGF1 dose titration in this population, further studies of GH/IGF1 dose relationships and potentially adverse metabolic outcomes are required. Future studies using biomarkers and genetic markers influencing GH/IGF1 might improve understanding of the heterogeneity and individualisation of treatment.

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