The Efficacy and Safety of Long-term Norditropin® Treatment in Children with Prader-Willi Syndrome

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- growth hormone
- Prader-Willi syndrome
- body composition
- height

Abstract

Prader-Willi syndrome is a genetic disorder that is associated with short stature, partial growth hormone deficiency, small hands and feet, learning and behavioural problems, and hyperphagia leading to severe, often morbid, obesity. Growth hormone therapy is associated with an improvement in height and body composition. We evaluated the efficacy and safety of long-term growth hormone treatment in a retrospective observational multinational study of 41 prepubertal children (mean age 3.8±3.0 years) with genetically diagnosed Prader-Willi syndrome treated with growth hormone (0.03–0.06 mg/kg/day) for >12 months [mean duration 4.1 (range 0.9–9.5) years]. Height, weight, and body composition measurements were recorded at baseline and at 6 month intervals until last observation. Mean (SD) gain in height at 12 months was 0.9 (0.2) SD score ($p<0.0001$). At last observation (after approximately 6 years) mean gain in height was 1.3 (0.3) ($p=0.0001$) with 85% of children achieving height > −2 SD score. Body composition improved during treatment with an estimated 9.1% increase in lean body mass and 9.1% decrease in fat mass at last observation ($p=0.019$). Scoliosis was reported in 3 patients at baseline and 8 patients at last observation. Sleep apnoea was recorded in 3 (7.3%) patients. There were no other severe adverse events reported. Long-term growth hormone treatment of prepubertal children with Prader-Willi syndrome was associated with significant improvements in height and body composition. Treatment was well tolerated. The development of scoliosis warrants monitoring by an orthopaedic specialist.

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Introduction

Prader-Willi syndrome (PWS), which affects between 1:20000 and 1:30000 live births [1,2], is a complex neurodevelopmental disorder caused by defects in chromosome 15 [3,4]. This disorder is characterised by short stature with small hands and feet, hypogonadism with incomplete pubertal development, and cognitive and behavioural problems [5]. Newborns and infants typically present distinct muscle hypotonia and failure to thrive, whereas later in life food seeking behaviour is usually predominant. Severe obesity may develop unless treated with a controlled diet and regular exercise [1]. Many symptoms of PWS have been linked to abnormal hypothalamic regulation, namely altered energy balance in conjunction with hyperphagia, hypoactivity, and hypogonadism. In addition, clinical observation of patients has shown reduced response to a growth hormone (GH) stimulation test in many individuals with PWS [6–8]. Obesity decreases GH secretion; however, in PWS patients it appears that the observed reduction in GH secretion is independent of increased body mass index (BMI) [6–8].

Many characteristics of PWS are also seen in patients with GH deficiency including short stature, reduced muscle mass, obesity, and delayed bone maturation. GH therapy has been shown to have a beneficial effect on both height and metabolic disorders in individuals with GH deficiencies and prior clinical studies have also demonstrated that short-term GH treatment increases height-for-age and improves body composition in children with PWS [9–12]. Growth velocity and body composition are further improved in PWS patients after long-term GH therapy (48 months) [13,14], and may lead to an adult height within the normal range [9]. However, these beneficial effects were seen to be dose-dependent with improvements in body

composition and growth velocity observed in children receiving GH doses of 1.0 or 1.5 mg/m^2/day, but not those treated with 0.3 mg/m^2/day [13].

This retrospective study was completed to evaluate the long-term efficacy and safety of GH treatment with Norditropin® (Novo Nordisk A/S, Bagsvaerd, Denmark) in children with PWS.

Subjects and Methods

Subjects

Pre-pubertal children (as assessed by Tanner stage 1 or testicular volume < 4 ml) with genetically diagnosed PWS were considered for this study. To be eligible for inclusion, children had to have received GH (Norditropin®, Novo Nordisk A/S, Bagsværd, Denmark) for at least 12 months and have height assessments at both baseline and 12 months; patients who had received only one injection could still be included in this study providing they had the required height assessments. Children who had received prior GH treatment before their first dose of Norditropin® were excluded. Written informed consent was obtained from the child's parents (or legal representatives). The trial was registered with ClinicalTrials.gov (NCT00705172) and was performed in accordance with the Declaration of Helsinki.

Trial design

This was a retrospective, observational, open-label, multicentre, multinational study completed at 3 investigational centres in Switzerland, Denmark, and Germany. All participants were identified by investigators at their clinics. As this was a retrospective study, only one contact visit was required to gain informed consent. No study drug was administered during this trial.

The first patient received GH on 8 November 1988 and the last patient study visit was 26 November 2008. Throughout the treatment period, the study participants received a once-daily subcutaneous injection of GH in the evening. As GH was used off-label in these children the dose administered was at the discretion of the physician and could be adjusted as deemed necessary throughout the treatment period.

Once written consent was obtained, each child was assigned a unique study number. Upon assignment, the child's medical data could then be transcribed into the case report forms by the investigator or study nurse. Participants could withdraw from the study at any time. Study protocol was approved by appropriate authorities according to local regulations.

Assessments and endpoints

Height, weight, and body composition measurements were recorded at baseline. Thereafter, assessments were made at 6 month intervals until last observation (defined as when data were last transcribed into the case report form). Height of participants (without shoes) was measured in metres. BMI SDS was calculated using the WHO child growth standards [15]. Dual energy X-ray absorptiometry (DEXA) scans, bioimpedance, or stable isotope dilution were used to assess body composition, providing data on whole body fat mass (kg), whole body lean mass (kg), and total body water (kg). Blood samples were taken for clinical laboratory assessments of HbA_{1c}, IGF-I, thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) and levels were recorded at baseline and every subsequent visit thereafter.

The primary endpoint was to investigate changes in height standard deviation score (HSDS) from baseline following 12 months' GH treatment in children with PWS (PWS population) [16]. Changes in body composition (12 months and last observation), height velocity (12 months and last observation), and HSDS (last observation) were the main secondary endpoints. Safety assessment included incidence of adverse events and levels of HbA_{1c}, TSH and IGF-I.

Statistical analysis

Untreated controls were not included in this study; instead, baseline data (obtained before initiation of treatment) were used as a control for primary and secondary endpoints together with growth references to untreated children with PWS [16] and normal children [17].

Primary efficacy analysis was performed on both the intention-to-treat (ITT) analysis dataset [comprised of participants who had completed at least 12 months' GH treatment (n = 41)] and the per-protocol dataset [including all children from the ITT set who had at least 80% compliance and no major protocol deviations (n = 38)]. Treatment effect on HSDS was tested using analysis of co-variance (ANCOVA) with age at treatment initiation, pubertal stage (Tanner stage), and baseline HSDS as covariates. Secondary endpoints were analysed using a similar method on the ITT dataset alone, at 12 months and last observation of GH treatment; last observation carried forward (LOCF) was applied to any missing post-baseline value. For the LOCF analysis, only patients who had been treated with GH for 12 months (±6 weeks) were included.

Results

Forty-one children with PWS (aged 0.4–12.2 years; mean: 3.8 years) were included in this study, all of whom were exposed to GH (see **Table 1** for baseline demographics). Treatment was discontinued before the end of the first year in 3 of the 41 children; 2 withdrew due to adverse events (sleep apnoea and enuresis; urinary tract infection and convulsion). The mean treatment duration was 4.1 years (range: 0.9–9.5 years), during which participants were treated with a mean GH dose of 0.03 mg/kg/day (up to 0.06 mg/kg/day).

After 12 months of GH treatment, an estimated mean (SD) gain in HSDS of 0.94 (0.12) ($p < 0.0001$) was achieved (standardised to the PWS population) (**Table 2**); neither baseline height (HSDS) nor pubertal stage had a statistically significant effect on the change in HSDS at 12 months. Many of the children achieved a height SDS above the normal range for the PWS population after 12 months (**Table 2**). At last observation (approximately 6 years), the mean (SD) increase in HSDS from baseline was 1.3 (0.3) SDS ($p = 0.0001$) with mean (SD) HSDS increasing from a baseline value of −0.3 (0.9) SDS to 1.1 (1.1) SDS.

When the data were standardised to the normal population similar results were seen, with an estimated mean (SD) gain in HSDS of 0.71 (0.16) ($p = 0.0001$) observed after 12 months of GH treatment, and a total gain in height of 1.1 (0.22) SDS ($p < 0.0001$) at last observation (**Table 2**). Overall, HSDS changed from a baseline value of −1.8 SDS to −1.2 SDS after 12 months and to −0.7 SDS at last observation. Baseline HSDS had a significant inverse effect on change in HSDS to last observation ($p < 0.0001$); that is, GH treatment had less effect on height gain in children who were taller at baseline. Baseline IGF-I was correlated ($p = 0.016$)

inversely with the 12-month height gain. Improvements in HSDS were reflected in the increased percentage of children with a HSDS within the normal range (above −2.0) following GH exposure from 46% at baseline to 66% after 1 year and 85% at last observation.

At baseline, girls were generally shorter than boys (median [range]) (referenced to a normal population: boys −1.5 [−4.4; 2.5] SDS; girls −2.5 [−3.6; 0.4] SDS) (**Table 3**). After the first year of treatment, the mean change in HSDS was not significantly different between the sexes (**Table 3**). At last observation (LOCF) mean overall height gain was greater for boys than for girls (**Table 3**). This between-gender difference was statistically significant when referenced to the normal population. Median (range) HSDS at last observation was −0.1 (−2.9; 1.5) for boys and −1.3 (−4.0; 0.5) for girls (referenced to normal population).

Table 1 Baseline characteristics (ITT dataset).

Characteristics	GH
Number of subjects	41
Mean age, years (range)	3.8 ± 3.0 (0.4–12.2)
Race, n (%)	
White	41 (100.0)
Country, n (%)	
Denmark	19 (46.3)
Germany	10 (24.4)
Switzerland	12 (29.3)
Sex, n (%)	
Female	19 (46.3)
Pre-pubertal stage, n (%)	
Yes	38 (92.7)
Weight, n	37
Mean weight, kg (range)	17.6 ± 17.8 (5.8–99.8)
BMI, n	38
Mean BMI, SDS (range)	0.6 ± 1.9 (−2.8–5.8)
Height, n	37
Mean height, cm (range)	90.6 ± 21.4 (58.0–145.0)
Height SDS, n	37
Mean height SDS (referenced to PWS population) (range)	−0.3 ± 0.9 (−2.4–2.4)
Height SDS, n	37
Mean height SDS (referenced to normal population) (range)	−1.8 ± 1.4 (−4.4–2.5)
HbA_{1c}, n	23
Mean HbA_{1c} (mmol/mol)	33.3 ± 4.4 (23.5–43.2)
IGF-I SDS, n	28
Mean IGF-I SDS	−1.4 ± 1.4 (−3.6–3.4)

Values are n (%) ± SD where appropriate. ITT: intention-to-treat

Body composition

A clinically significant improvement in body composition was seen in children with PWS following GH treatment. After 12 months, an estimated increase in percent lean body mass of 9.9% was achieved (p = 0.017). A corresponding 9.9% decrease in percent fat mass was also reported. This related to an actual increase in lean body mass of 3.3 kg and a decrease in fat mass of 0.2 kg from baseline. These results were sustained throughout drug exposure with an estimated 9.1% increase in percent lean body mass and 9.1% decrease in percent fat mass at last observation (p = 0.019). Exploratory analyses suggest a negative, nonsignificant, correlation between age at treatment start and the percentage change in lean body mass during GH treatment (correlation at 12 months, p = 0.45; LOCF, p = 0.12), with older children showing less change in lean body mass than younger children during GH treatment. There was no effect of baseline age on the mean change in body composition. When reporting these data it should be noted that baseline body composition data were only available for 11 of the 41 children included in this study. Variations in data across the 11 children could potentially be explained by their duration of exposure to GH, degree of obesity, and possibly age at treatment initiation.

Safety

During treatment exposure, 128 adverse events were reported in the safety population [all patients exposed to GH (n = 41)]; 31 children were affected. The majority of adverse events were mild or moderate in severity and were deemed unlikely to be related to treatment with the study drug by investigators. Respiratory tract infections (affecting 14.6% of the children) and scoliosis (affecting 19.5%) were the most frequent adverse events; other events were seen at a low frequency in 1 or 2 participants. Of the total number of adverse events reported, 33 events (in 17 children) were possibly related to GH treatment. Scoliosis and

Table 2 Changes from baseline in HSDS.

Reference population	Mean HSDS (SD)			Estimated mean gain in HSDS (SD)	
	Baseline	1 year	Last observation	1 year	Last observation
PWS children	−0.3 (0.9)	0.7 (0.9)	1.1 (1.1)	0.9 (0.2) p < 0.0001	1.3 (0.3) p = 0.0001
Normal children	−1.8 (1.4)	−1.2 (1.2)	−0.7 (1.2)	0.7 (0.2) p = 0.0001	1.1 (0.2) p < 0.0001
HSDS > −2.0, n (%)	19 (46)	27 (66)	35 (85)	–	–

Table 3 Changes from baseline in HSDS by gender.

Reference population	Mean HSDS (SD)			Estimated mean gain in HSDS (SD)	
	Baseline	1 year	Last observation	1 year	Last observation
PWS children					
Girls (n = 19)	−0.3 (0.7)	0.6 (0.8)	0.7 (1.1)	0.9 (0.5)	1.1 (1.0)
Boys (n = 22)	−0.1 (1.1)	0.8 (1.0)	1.3 (1.0)	0.8 (0.5)	1.4 (1.3)
Difference (girls–boys)				p = 0.2164	p = 0.1737
Normal children					
Girls (n = 19)	−2.1 (1.3)	−1.6 (1.2)	−1.3 (1.1)	0.6 (0.7)	0.8 (1.1)
Boys (n = 22)	−1.5 (1.5)	−0.9 (1.2)	−0.2 (1.1)	0.8 (1.5)	1.3 (1.3)
Difference (girls–boys)				p = 0.3522	p = 0.0042

Table 4 Serious adverse events [safety dataset (n = 41)].

	n	GH (%)	E
Total events	7	17.1	10
Respiratory, thoracic, and mediastinal disorders	4	9.8	4
Status asthmaticus	2	4.9	2
Apnoea	1	2.4	1
Snoring	1	2.4	1
Infections and infestations	3	7.3	4
Cryptosporidiosis infection	1	2.4	1
Gastroenteritis	1	2.4	1
Tonsillitis	1	2.4	1
Urinary tract infection	1	2.4	1
Musculoskeletal and connective tissue disorders	1	2.4	1
Scoliosis	1	2.4	1
Nervous system disorders	1	2.4	1
Febrile convulsion	1	2.4	1

n: number of subjects; E: number of events

sleep apnoea were the most frequent of these, affecting 19.5 and 7.3 % of children, respectively. Serious adverse events included respiratory disorders, infections, and nervous system disorders (see **Table 4** for more details). Of these, tonsillitis, snoring, and scoliosis were assessed as possibly related to GH exposure.

All 8 cases of scoliosis reported (7 of which were mild or moderate in severity) were assessed as possibly linked to GH treatment. Despite this potential link to the study drug, no dosing alterations were made following the onset of scoliosis. Furthermore, there was no report of aggravation of the condition during drug exposure. Scoliosis incidence in study participants was not entirely unexpected as this condition is often seen in patients with PWS and at least 3 of the children reporting scoliosis during the study period presented with the condition at baseline.

Two children discontinued GH treatment due to adverse events. One reported sleep apnoea and enuresis and discontinued treatment after 90 days, the other terminated GH treatment after 2.4 years following a severe urinary tract infection and convulsions. Both recovered fully. No deaths were reported during the study period.

During the first year of GH treatment, IGF-I SDS rose steadily from a baseline value of −1.4–1.0. IGF-I SDS stabilised at this higher value for the remainder of the treatment period; at year 1 the change in IGF-I SDS from baseline was 2.2 compared with 2.1 at last observation. The mean values of IGF-I SDS recorded were within the reference range; however, at one or more time points, individual values were above the reference range with 7 children displaying temporary or consistently high IGF-I SDS levels. Laboratory assessments revealed no clinically relevant changes in glucose metabolism (as evaluated by assessment of HbA_{1c}), haematology or thyroid parameters during the observation period. There were no thyroid- or haematology-related adverse events reported.

Discussion

In this retrospective, observational study, administration of GH for 12 months resulted in the normalisation (or near-normalisation) of height in children with PWS, with 66 % of participants reaching a height within the reference range for normal children. Further improvements were seen with continued GH treatment with 85 % of children reaching a height within the reference range for normal children at last observation. These results indicate that GH use in children with PWS is effective in treating short stature. Other clinical studies have shown similar results following GH therapy in the PWS population [9–12, 18]. Data from the KIGS database (the Pfizer international growth database) revealed a median increase in height SDS of 0.88 after 1 year and 1.32 after 2 years of GH treatment [12]. From the KIGS data, it appears that the age at which patients initiate GH therapy could affect clinical outcomes; the effect of GH therapy on HSDS was more significant in patients receiving treatment at a younger age. Furthermore, in the present study exploratory analyses suggest that baseline IGF-I levels may be inversely related to the gain in height associated with GH therapy.

In addition to their short stature, patients with PWS often have abnormal body composition; increased fat mass and decreased lean body mass are characteristic of this population [19, 20]. As a consequence of GH deficiency and abnormal hypothalamic regulation causing hypoactivity and insatiable hunger, muscle mass is decreased by 25–37 % in individuals with PWS, which may partly explain the weakness and hypotonia in these patients [20, 21]. Fat mass is increased, culminating in massively increased levels of obesity in this population, which has been associated with elevated morbidity and mortality of PWS patients [22].

In this study, GH treatment was seen to improve body composition with actual increases in lean body mass and concurrent reductions in fat mass observed after 12 months. These improvements were sustained until last observation after approximately 6 years. It should be noted when discussing these results that body composition data was only available for 11 out of the 41 children included in this study. Despite this, the trend for improved body composition in this study is in line with data from other long-term clinical trials using GH to treat PWS [14, 18, 19]. In a study by de Lind van Wijngaarden et al., body fat percentage SDS was significantly lower than baseline after 4 years of GH treatment ($p < 0.0001$) [14]. By contrast, the improvements in lean body mass were not sustained; the significant increases in lean body mass observed after the first year of treatment disappeared during the second year with values returning to baseline values. This suggests that the clinical benefits of GH replacement on body composition may depend on a number of variables in addition to GH. Exploratory analyses suggest there may be a negative correlation between change in lean body mass and age at treatment start, with the response being greater in younger as compared with older children. Further investigations will be needed to clarify these data. The comprehensive care package offered to patients with PWS and their families encompassing the restriction of caloric intake, increased physical activity and patient and family education [23] may explain sustained GH-related benefits on body composition.

Data from the present study demonstrate that GH is safe for use in children with PWS and no major safety concerns were revealed. The majority of adverse events reported during the study were assessed as not related to the study drug. Of those deemed to be linked to GH, scoliosis was most frequently observed. However, the 8 cases of scoliosis reported (7 of which were reported as not serious) were not unexpected as this condition is often seen in patients with PWS [18, 24–26]. Furthermore, scoliosis was present in at least 3 children at baseline. As found by others [18, 25, 26], GH treatment was not seen to aggra-

vate the condition and no dose adjustments were thought necessary.

In summary, GH treatment was well-tolerated in children with PWS and led to significant improvements in both height and body composition. No new safety concerns were raised as a result of this study.

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Conflict of Interest

Fabian Schmidt and Anne-Marie Kappelgaard are employees and shareholders of Novo Nordisk. Jens Sandahl Christiansen is a recipient of an unrestricted research grant from Novo Nordisk, has taken part in an Advisory Board and given talks on growth hormone at Novo Nordisk sponsored events. Udo Meinhardt, Constanze Lämmer, John Østergaard, and Urs Eiholzer have no conflicts of interest to declare.

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