Long-Term Efficacy and Safety of Two Doses of Growth Hormone in Short Japanese Children Born Small for Gestational Age

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Abstract
Background/Aims: To investigate the long-term efficacy and safety of two doses (33 and 67 μg/kg/day) of growth hormone (GH) in short Japanese children born small for gestational age (SGA).

Methods: 96 children born SGA (age 3 to <8 years) were randomized to GH at 33 or 67 μg/kg/day for 104 weeks, or to an untreated control (UC) group for 52 weeks. After 52 weeks, the UC group was randomized to GH at a dose of 33 or 67 μg/kg/day for a 156-week extension study. Initial treatment groups continued unchanged for the extension phase. Efficacy was evaluated by change in height SDS for chronological age from baseline to 208/260 weeks.

Results: After 208 weeks, change in height SDS from baseline (least square (LS) means (SE)) was 1.01 (0.47) and 1.99 (0.67) in the UC 33 and UC 67 μg/kg/day groups, respectively. After 260 weeks, change in height SDS from baseline was 1.22 (0.51) and 2.01 (0.64) in the 33 and 67 μg/kg/day groups, respectively. Insulin-like growth factor-1 levels were significantly higher in the groups receiving 67 μg/kg/day but largely remained within normal limits (~2 to +2 SDS).

Conclusions: Long-term continuous GH treatment was well tolerated and effective in improving height SDS. Improvements were dose-dependent and significantly higher at 67 than 33 μg/kg/day.

Introduction

Small for gestational age (SGA) at birth is a relatively common condition, with approximately 5% of all newborns being below −2 standard deviation scores (SDS) for weight and/or length [1]. While the majority of these children will demonstrate catch-up growth in early life, approximately 10% of children born SGA will fail to do this by 2 years of age [2, 3]. This height deficit continues into adulthood, with final adult heights remaining below −2 SDS of mean height [1, 4].

There are three main alterations in growth hormone (GH) or insulin-like growth factor-1 (IGF-1) levels that are found in children with short stature born SGA: (i) low levels of GH plus low levels of IGF-1, IGF-2, and insulin-like growth factor-1 levels were significantly higher in the groups receiving 67 μg/kg/day but largely remained within normal limits (~2 to +2 SDS).

This paper is dedicated to the late Professor Kenji Fujieda.
like growth factor binding protein-3 (IGFBP-3); (ii) normal levels of GH but low levels of IGF-1 and IGFBP-3 suggesting a decreased GH sensitivity, and (iii) decreased IGF-1 sensitivity, as shown by high/normal levels of GH and IGF-1 [5]. High-dose exogenous GH might be able to induce catch-up growth in children with any of these alterations. Indeed, GH therapy improves height velocity (HV) and height SDS at adult height in patients with short stature who are born SGA.

However, the literature is still divided over the best dosing regimen for GH therapy in SGA. Moreover, GH treatment results in reversal of the low IGF-1 levels seen in children with SGA. While this has benefits – low IGF-1 is associated with abnormalities in body composition, aberrant metabolism and increases in cardiovascular risk factors [6, 7] – there have been concerns that high levels of IGF-1 may result in an increased risk of malignancies [8]. Current guidance suggests that IGF-1 SDS should be no greater than 2 SD above the mean. Consequently, this study was conducted with the aim of comparing the efficacy and safety of two continuous dosing regimens in promoting catch-up growth and IGF-1 levels over the study period.

This was a 156-week extension study of an initial 104-week multicenter, randomized, double-blind, and parallel-group trial (trial registration No. JapicCTI-050132, NCT00184717) investigating the efficacy and safety of two doses of Norditropin® (Novo Nordisk A/S, Denmark) (NN-220) in subjects with short stature born SGA. The total exposure time to NN-220 was 208 and 260 weeks, respectively.

**Patients and Methods**

**Patients**

The study population was composed of short SGA children. Since the definition of SGA in Japan is newborns being below the 10th percentile of gestational age for both birth weight and birth length, inclusion criteria were as follows: (i) SGA with birth weight and birth length <10th percentile of gestational age; (ii) SGA with birth weight SDS or birth length SDS ≤−2 SDS for gestational age; (iii) height SDS for chronological age ≤−2 SDS; (iv) chronological age: boys 3 to <8 years, girls 3 to <7 years; (v) peak GH level of >10 ng/ml in at least one GH provocation test conducted within 1 year prior to Visit 1; (vi) HV SDS for chronological age in 1 year prior to Visit 1 (screening visit) of <0 SDS, and (vii) prepubertal children (Tanner stage 1 for both boys and girls).

Exclusion criteria included children with known or suspected allergy against GH or related products (including any component of the trial products); children with serious heart disease, renal disease or hepatic disease; children with diabetes; children with a history or presence of malignancy and/or who had been treated with radiotherapy or chemotherapy. Children who had previously received GH treatment or systemic thyroid hormone, androgen, estrogen, progesterone, anabolic steroid, adrenocortical steroid (except temporary use), analogue of gonadotropin-releasing hormone, and IGF-1 (within 2 years of this trial) were not eligible. Furthermore, children with endocrine diseases, with chromosomal abnormalities or with systemic bone diseases that lead to short stature were also excluded.

The trial was performed in accordance with the Declaration of Helsinki and written informed consent was obtained from the subjects themselves or the subjects’ parent/legal guardians.

**Study Design**

Patients were initially randomized to one of two GH treatment groups: GH 33 or 67 μg/kg/day for 104 weeks, or to an untreated control (UC) group. After 52 weeks, the UC group was randomized into two treatment groups of GH 33 or 67 μg/kg/day for a further 156 weeks. This was done to give those in the untreated group an opportunity to receive GH. At 104 weeks, those initially randomized to a treatment group in the original trial continued for a further 156 weeks of treatment with the same GH dose.

Results of the initial 104-week treatment phase of the two dose groups compared with the UC group at 52 weeks have been published [9].

The trial product doses (5 and 10 mg/1.5 ml) were confirmed indistinguishable from one another and the package box of the trial products was assigned a randomization number and blinded by the person responsible for randomization. Both doses of the trial product were injected using NordiPen® (Novo Nordisk A/S) to maintain blinding. Subjects were given a unique subject number written in his/her informed consent and were randomized centrally via minimization [10] and stratified according to age (<6 and ≥6 years old).

The primary aims of the trial were to evaluate the long-term efficacy of two doses of GH (33 and 67 μg/kg/day) as assessed by change in SDS for chronological age from baseline to 260-/208-week treatment in subjects with short stature born SGA, and to evaluate the degree of change in IGF-1 SDS from baseline to 208/260 weeks for each dose. The secondary objectives were to compare the yearly HV SDS for chronological age, change in IGF-1 concentrations (Δ IGF-1) from baseline to 260/208 weeks, and the safety profile of NN-220 (33 and 67 μg/kg/day) as assessed by adverse events, clinical laboratory tests, oral glucose tolerance test, HbA1c (glycosylated hemoglobin A1c) and bone age.

**Statistical Analysis**

All efficacy analyses were performed on the Full Analysis Set consisting of all randomized patients with efficacy data after treatment start. Change in height SDS from baseline during treatment was analyzed by analysis of variance (ANOVA), with baseline height SDS for chronological age and chronological age as covariates. Secondary endpoints were analyzed using the same statistical model. All tests were two-sided and a significance level of 5% was used and confidence intervals (CI) were constructed with a confidence limit of 95%.

Sample size of the initial trial was determined from a previous report [11] assuming a dropout rate of 30% and with 80% power. Consequently, 19 cases would be required in the control group, 35 cases in the 33 μg/kg/day group and 35 cases in the 67 μg/kg/day group.
**Results**

**Patient Demographics**

A total of 92 patients completed the initial trial, 20 patients in the 52-week control group, and 36 patients in both 104-week treatment groups. Of these, 86 patients enrolled in the extension (6 patients in the initial treatment groups did not continue) (fig. 1). Patient characteristics at baseline did not differ between groups (table 1).

**Height SDS**

After 208 weeks (4 years), mean (SD) height SDS was −1.95 (0.82) in the UC 33 µg/kg/day group and −0.76 (0.75) in the UC 67 µg/kg/day group (p < 0.042) (fig. 2). The change in height SDS from baseline to 208 weeks last observation carried forward (LOCF), LS mean (SE) was 1.01 (0.47) and 1.99 (0.67) in the UC 33 and UC 67 µg/kg/day groups, respectively. After 260 weeks (5 years), mean (SD) height SDS was −1.78 (0.78) in the 33 µg/kg/day group and −0.82 (0.74) in the 67 µg/kg/day group (p < 0.001) (fig. 2). The change in height SDS from baseline to 260 weeks (LOCF, LS mean (SE)) was 1.22 (0.51) and 2.01 (0.64) in the 33 and 67 µg/kg/day groups, respectively.
Height Velocity SDS

HV SDS increased from baseline, with greater gains in the 67 μg/kg/day groups. The increase in HV SDS was greatest during the first 52 weeks of treatment for all groups (fig. 3). Mean HV SDS for the 67 μg/kg/day group was 1.47 at 4 years falling to 0.80 at 5 years. In the 33 μg/kg/day group, mean HV SDS was 0.40 and 0.46, respectively during this period. After 208 weeks, the UC 33 and 67 μg/kg/day groups had a mean HV SDS of 0.54 and 2.19, respectively. The persistence of values above zero suggests that catch-up growth was continuing in all treatment groups.

IGF-1

Significant increases in IGF-1 levels were seen with GH treatment over 5 years. The change in IGF-1 from baseline to 260 weeks (LOCF, LS mean (SE)) was 342.2 (42.6) and 547.4 (41.9) ng/ml for the 33 and 67 μg/kg/day groups, respectively (estimated mean difference (95% CI) of 205 (85, 325) ng/ml, p < 0.01) (table 2).

Analysis of IGF-1 SDS showed a rapid increase in IGF-1 in the first 4 weeks, which was then maintained at a fairly constant level throughout the treatment period. After 260 weeks, the mean IGF-1 SDS was significantly higher in the group receiving 67 μg/kg/day (0.77 and 1.72 for the 33 and 67 μg/kg/day groups, respectively,
Long-Term Efficacy and Safety of GH in Short Japanese Children Born SGA

IGF-1/IGFBP-3 Molar Ratio

Baseline IGF-1/IGFBP-3 molar ratios were 0.21 and 0.20 in the 33 and 67 μg/kg/day groups, respectively. By completion of treatment at 260 weeks, IGF-1/IGFBP-3 molar ratios had increased to 0.54 in the 33 μg/kg/day group and 0.71 in the 67 μg/kg/day group. A similar pattern was observed in the UC 33 and UC 67 μg/kg/day groups. After 208 weeks, increases from 0.22 and 0.21 to 0.57 and 0.67 were observed in the UC 33 and 67 μg/kg/day groups, respectively.

Adverse Events and Glycemic Parameters

Both doses of GH were well tolerated and few adverse events were considered related to GH treatment. The majority of adverse events were mild-to-moderate infections unrelated to the trial product. Adverse events that were judged probably related to the trial product were predominantly from the musculoskeletal and connective tissue disorders system organ class, and included arthralgia and pain in the extremities. These adverse events were considered a result of accelerated growth and were more frequently reported in the high-dose groups.

After 260 or 208 weeks, profiles of blood glucose in oral glucose tolerance test remained almost unchanged from the baseline while blood insulin levels increased slightly. No subjects were categorized as diabetic type-1 during the treatment period. After 260 weeks of treatment, slight but significant increases from baseline in HbA1c were observed in both the 33 and 67 μg/kg/day groups, with an estimated mean (95% CI) of 0.18% (0.09, 0.26) and 0.32% (0.26, 0.38), respectively. A significant difference between the two groups was observed, with an estimated mean difference (95% CI) of 0.14 (0.4, 0.24). HbA1c appeared to slightly increase during the initial 2 years and then remained at the same level until 260 weeks. No subject had an HbA1c above the reference range (4.3–5.8%) during the treatment period. When compared with

### Table 2. IGF-1 levels at baseline and after treatment (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>260 weeks (LOCF)</th>
<th>208 weeks (LOCF)</th>
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<tbody>
<tr>
<td>33 μg/kg/day (n = 28)</td>
<td>121.58 ± 49.12</td>
<td>465.43 ± 190.52</td>
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<tr>
<td>67 μg/kg/day (n = 29)</td>
<td>120.07 ± 49.73</td>
<td>665.86 ± 319.30</td>
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<tr>
<td>UC 33 μg/kg/day (n = 7)</td>
<td>145.63 ± 43.50</td>
<td>508.29 ± 268.55</td>
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<tr>
<td>UC 67 μg/kg/day (n = 8)</td>
<td>153.50 ± 62.99</td>
<td>677.88 ± 342.07</td>
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</table>

**Fig. 3.** HV for chronological age during the study period by treatment group.

p = 0.0114). IGF-1 SDS was also consistently higher in the UC 67 μg/kg/day group compared to the UC 33 μg/kg/day group. Although the initial increase in IGF-1 was highest for the UC 67 μg/kg/day group, this was not significantly different from the 67 μg/kg/day group. In the UC 67 μg/kg/day group, between weeks 12 and 39, the IGF-1 SDS exceeded the upper normal range (2 SD above the mean). This was not seen in any of the other groups including the 67 μg/kg/day group, and may reflect the smaller sample size of the UC 67 μg/kg/day group (n = 8) compared to the 67 μg/kg/day group (n = 29). Nevertheless, this level of IGF-1 was not consistent in the long term and by week 130 had stabilized at a lower level (fig. 4).
baseline levels, there was a slight but significant increase in AUC_\text{glucose} \text{ (at 208 or 260 weeks)} in the 33 μg/kg/day group and a slight but significant increase from baseline in HbA_1c was observed for both the 33 and 67 μg/kg/day groups.

Anti-Human GH Antibodies

Anti-human GH antibody test positives were observed for a total of 4 subjects in the 33 μg/kg/day group and 9 subjects in the 67 μg/kg/day group. One subject in the UC 33 μg/kg/day group developed anti-human GH antibodies. The formation of antibodies did not appear to affect height SDS in any of these subjects.

Bone Age

Mean (SD) increase in bone age during 260 weeks was 5.79 (1.05) years for the 33 μg/kg/day group and 7.15 (1.05) years for the 67 μg/kg/day group. At 260 weeks, mean bone age/chronological age was approximately 1 in both groups: 1.012 (0.13) and 1.086 (0.098) for the two groups, respectively. Mean (SD) increase in bone age during 208 weeks was 6.54 (1.26) years for the UC 33 μg/kg/day group and 5.60 (1.68) years for the UC 67 μg/kg/day group. At 208 weeks, mean bone age/chronological age was approximately 1 in both groups: 1.048 (0.15) and 1.015 (0.185) for the two groups, respectively.

Discussion

This study demonstrated the efficacy and safety of up to 5 years of two doses of human GH (33 and 67 μg/kg/day) in the treatment of Japanese children with short stature born SGA. Both doses resulted in statistically significant dose-dependent increases in height SDS. The patient demographics of the population at baseline indicated that the children were of shorter stature, had slower HV and a delay in bone age than the reference population and were therefore considered representative for children born SGA without catch-up growth.

The dose-dependent growth-promoting effect of human GH treatment observed here is consistent with results from European studies involving short children born SGA [11–15]. This study adds to the few publications that have investigated GH treatment over longer periods of time (3–12 years) for children born SGA [15–17]. These European studies indicate that children born SGA will reach a normal adult height with long-term continuous GH treatment. Results from our study show that this may also be true in Japanese children born SGA as catch-up growth was continuing at 208 weeks of treatment with 67 μg/kg/day. Also consistent with findings from European studies is the observation that HV was slower in the second year.
of treatment compared to the first year of treatment. In a
2-year study conducted in Germany of 69 prepubertal
children born SGA allocated to no treatment or GH treat-
ment at 0.1 or 0.2 IU/kg/day (33 or 67 ,ug/kg/day), mean
HV SDS after the first year of treatment was –1.2, 2.8 and
5.5, respectively [18]. Slower HV was seen during the se-
cond year with corresponding values of –0.9, 1.6 and 2.9,
respectively. This is also a consistent finding with GH
therapy in other indications, for example Turner syn-
drome and GH deficiency.

Given the potential association of high circulatory
IGF-1 levels and cancer risk, we conducted detailed mea-
surements of the change in IGF-1 throughout the course
of the study. In the UC 67 ,ug/kg/day group, IGF-1 SDS
marginally exceeded the recommended guidelines for a
period of 27 weeks (the highest IGF-1 SDS being 2.26).
However, as the study progressed, the IGF-1 levels in this
group stabilized at a lower level, within the normal range.
A dose of 33 ,ug/kg/day resulted in significantly smaller
increases in IGF-1 SDS; however, the improvement in
growth, although still significant, was not as great as with
the higher GH dose. It may therefore be prudent to adhere
to a lower GH dose, particularly in patients who may be
predisposed to certain cancer types. This represents a
compromise between achieving sufficient growth and
preventing unnecessary exposure to potential risk.

The molar ratio of IGF-1/IGFBP-3 is considered to re-
present the availability of free IGF-1 which can act to stim-
ulate growth. It has therefore been suggested that moni-
toring this ratio may aid in evaluating GH efficacy and
ulate growth. It has therefore been suggested that moni-
toring this ratio may aid in evaluating GH efficacy and

with early onset of puberty as an AE were observed. This
is in concordance with other studies that have shown GH
treatment does not affect the age of puberty onset in SGA
children, and that SGA children do not start puberty at a
younger age compared to normal statured children born
SGA [20, 21].

GH treatment in the study was generally well tolerated
in the long term with the majority of adverse events being
infections. As the number of adverse events appeared to
be higher in the high-dose group compared to the low-
dose group, further long-term monitoring for adverse
events may still be needed in subjects undergoing long-
term continuous GH treatment.

The blood glucose profiles from the oral glucose toler-
ance test did not appear to change over 4 years of treat-
ment; HbA1c appeared to increase continuously for the
first 2 years but then remained at the same level until 208
weeks. This is similar to the tolerability and safety of GH
treatment reported in European studies of short stature
children born SGA [11, 22].

Conclusion

This study demonstrates that long-term continuous
GH treatment was effective in improving height SDS in
short prepubertal Japanese children born SGA. After 260
weeks, gain in height SDS was significantly greater with
GH at a dose of 67 ,ug/kg/day than at 33 ,ug/kg/day. IGF-
1 SDS were significantly higher in children receiving 67
,ug/kg/day, but largely remained within the normal range.
Overall, GH treatment was safe and well tolerated in this
patient population.

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