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Response to growth hormone in very young children (<2 years) with growth hormone deficiency compared with prepubertal children aged ≥2 years: data from the NordiNet® International Outcome Study and ANSWER Program

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Objectives

- To compare the effectiveness and safety of growth hormone (GH) replacement therapy in children aged <2 years and prepubertal children aged ≥2 years.
- To compare the proportion of GH deficiency (GHD) and additional pituitary deficiencies in children aged <2 years vs ≥2 years.

Introduction

- GHD is a rare condition and difficult to diagnose in young children, as short stature is generally not the presenting feature.[1]
- Limited information is available on how very young children with GHD respond to GH treatment.[2]
- Two long-term observational studies were evaluated together to study the effectiveness of Norditropin® (somatropin; Novo Nordisk A/S) in young children as prescribed in a real-world clinical setting.

Methods

- The NordiNet® International Outcome Study (IOS; NCT00960128) was a multicentre study carried out in 23 countries from 2006 to 2016.
- The ANSWER Program (NCT01009905) was a multicentre study conducted in the USA from 2002 to 2016.
- GH treatment-naïve paediatric patients were divided into two age groups at baseline: <2 years vs prepubertal ≥2 years of age.
- The effectiveness and safety of the GH therapy were evaluated after 1 year of treatment.
- Height standard deviation score (SDS) and target height SDS were calculated based on national standards (NordiNet® IOS) or the US Centers for Disease Control (CDC) standard (ANSWER Program).
- Height velocity SDS was calculated based on World Health Organization standards for children aged <2 years,[3] EU standards for ages 2–6 years[4] and US standards for children aged >6 years.[5]

Results

Baseline

- The study groups comprised 506 children <2 years and 9810 children ≥2 years.
- Of the younger patient group, 43 (8.5%) were <2 months old at baseline.
- The younger children had numerically lower height SDS, higher height velocity SDS, and a lower GH peak compared with older children (**Table 1**).
- Mean insulin-like growth factor I (IGF-I) SDS was below 0 in both groups and lower in older vs younger children. GH dose was similar between groups at baseline (**Table 1**).

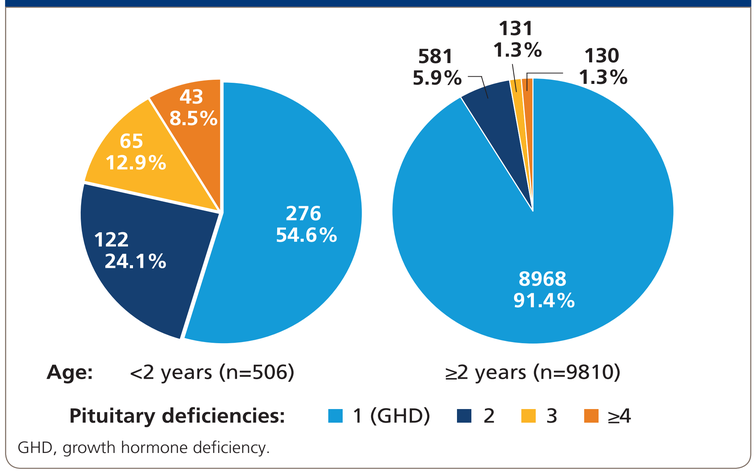
Table 1 ♦ Baseline characteristics

	Age <2 years		*Age ≥2 years*	
	n	*Mean (SD)*	*n*	*Mean (SD)*
Total	506		9810	
Male, %	302	59.7	6802	69.3
Age at treatment start, years	506	1.11 (0.57)	9810	9.09 (3.40)
Bone age/chronological age	76	0.86 (0.99)	4712	0.81 (0.18)
Height SDS[a]	506	–2.55 (1.77)	9810	–2.39 (1.01)
Height SDS for bone age[a]	47	–0.65 (3.05)	2722	–0.53 (1.63)
Target height SDS[a]	395	–0.20 (0.98)	8905	–0.57 (1.02)
GH peak, ng/mL	191	4.07 (4.78)	4864	5.45 (4.68)
GH dose, mg/kg/day	506	0.035 (0.014)	9810	0.037 (0.011)
IGF-I SDS[b]	253	–1.34 (1.07)	5875	–1.71 (1.59)
IGFBP-3 SDS[c]	121	–1.28 (1.35)	2772	–1.27 (1.72)
Birth weight, g	472	3033.3 (680.7)	8873	3032.3 (697.1)
Birth length, cm	381	48.3 (3.8)	6909	48.9 (3.9)
Mid-parental height, cm	396	171.3 (10.4)	8936	170.0 (13.6)
Height velocity, cm/year	45	13.89 (5.00)	1135	5.14 (2.14)
Height velocity SDS	45	0.26 (1.64)	1134	–0.94 (1.80)

[a]National standard used for NordiNet® IOS patients and CDC standard used for ANSWER patients.
[b]Calculated based on age and sex-related normative data[6].
[c]Calculated based on age and sex-related normative data[7].
GH, growth hormone; IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor-binding protein 3; SD, standard deviation; SDS, standard deviation score.

- A higher proportion of younger children (45.5%) was diagnosed with multiple pituitary deficiencies than older children (8.5%) (**Figure 1**).
- Proportionally more of younger children (73.2%, n=183) had abnormal MR imaging than older children (20.8%, n=3572).

Figure 1 ♦ Prevalence of diagnosed pituitary deficiencies within two groups of paediatric patients at baseline



GHD, growth hormone deficiency.

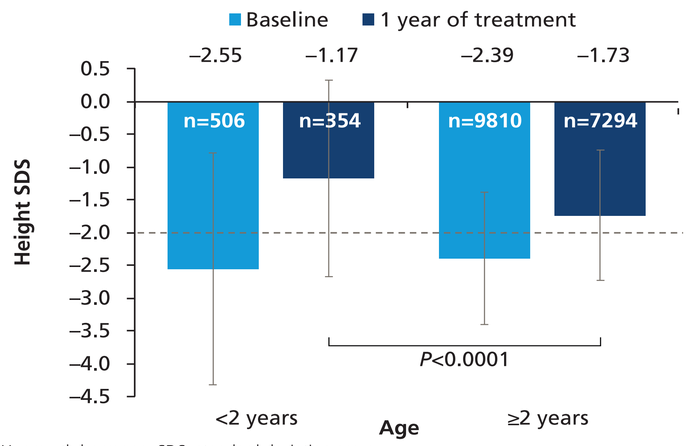
Effectiveness

- After one year of GH treatment, height SDS of both groups was within the normal range (SDS>–2) (**Figure 2**).
- In younger children, the increase in height SDS from baseline (mean [SD] 1.44 [1.22]) was more than twice that in older children (0.67 [0.49]).
- Height velocity SDS markedly improved in older children (mean [SD] 2.36 [2.07]) compared with younger children (mean [SD] 1.76 [1.75]).
- IGF-I SDS increased from baseline values below 0 to values above 0 in both groups.
- Mean GH dose was not changed from the start to 1 year of treatment.

Safety

- Treatment-related adverse reactions (ARs) occurred in 1.78% of young and 1.83% of older children.
- Serious ARs (SARs) were more prevalent in the younger group (0.79%) vs the older group (0.45%).
  - In children <2 years, the most frequent SARs (events/patients) included restlessness (2/1), screaming (2/1) and sleep disorder (2/1).
  - In children ≥2 years, the most common SARs were headache (6/6), raised intracranial pressure (6/5), scoliosis (4/3) and hyperglycaemia (4/3).
- Serious adverse events (SAEs) considered unrelated to treatment occurred in 4.35% of young and 0.93% of older children.
- Four deaths unlikely related to the treatment occurred, published in full elsewhere.[8]

Figure 2 ♦ Height SDS at baseline and after 1 year of GH replacement therapy. Grey dotted line denotes the lower bound of the normal range



GH, growth hormone; SDS, standard deviation score.

Conclusions

- Children aged <2 years who required GH replacement had more severe GHD than older children, as indicated by lower mean GH peak levels in stimulation tests.
- A higher proportion of younger children were diagnosed with additional pituitary deficiencies than older children; therefore, it is important to test for these additional deficits at diagnosis and during follow-up.
- GH therapy was associated with a rapid catch-up in growth in children <2 years, which emphasises the value of early diagnosis and treatment.
- The occurrence of treatment-related ARs was similar between the age groups; unrelated SAEs were more common in children <2 years. The safety profile was consistent with data in the approved labelling for Norditropin®.

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Conflict of interest disclosure

The authors have received attendance fees, compensation for travel expenses, speaker honoraria and/or consultancy fees from, or are employees of (VO, AP), Novo Nordisk, the sponsor of the NordiNet® International Outcome Study.

This study was supported by Novo Nordisk. NordiNet® IOS is registered at ClinicalTrials.gov (NCT00960128). The ANSWER Program is registered at ClinicalTrials.gov (NCT01009905). The authors thank the investigators and patients participating in this study. The authors take full responsibility for the content of the poster but are grateful to Watermeadow Medical (supported by Novo Nordisk Health Care AG) for writing assistance.
Presented at the 58th Annual Meeting of the European Society for Paediatric Endocrinology, Vienna, Austria, 19–21 September 2019.