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The association between growth hormone dose and short-term height outcomes in a large cohort of paediatric patients with Turner syndrome: real-world data from the NordiNet[®] International Outcome Study (IOS) and the ANSWER Program

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Objective

To analyse the impact of growth hormone dose on short-term height outcomes in a large cohort of paediatric patients with Turner syndrome.

Introduction

- The aims of growth-promoting therapy in girls with Turner syndrome (TS) are to optimise height during childhood and adulthood to minimise the physical restrictions of short stature, and to allow puberty to start at a similar age to peers.¹
- Clinical practice guidelines recommend a growth hormone (GH) dose of 45–50 µg/kg/day, increasing to 68 µg/kg/day, in individuals with poor height prognosis.¹ Current prescribing information for Norditropin[®] (somatotropin; Novo Nordisk A/S, Denmark) states a maximum dose of 67 µg/kg/day.
- Norditropin[®] is indicated for the treatment of children with short stature associated with TS, as well as a number of other conditions (approved indications vary among countries).
- Real-world data on the modifiable factors influencing near-adult height outcomes in GH-treated patients with TS are limited, but short-term responsiveness to GH treatment is a candidate.²
- We analysed the impact of GH dose on short-term (up to 2 years) height outcomes in a large cohort (n=1125) of paediatric patients with TS.
- This analysis used pooled data from two complementary, non-interventional, multicentre studies: the NordiNet[®] International Outcome Study (IOS) (NCT00960128) and the ANSWER Program (NCT01009905).
 - NordiNet[®] IOS and the ANSWER Program evaluated the long-term effectiveness and safety of Norditropin[®], as prescribed by treating physicians in a real-world clinical setting.

Methods

- The design and methodology of NordiNet[®] IOS and the ANSWER Program have been published previously.³ Patient information was entered by participating physicians using a web-based system, and Norditropin[®] was administered according to routine practice and local regulations.
- In both studies, paediatric patients were eligible if they had an appropriate diagnostic indication for Norditropin[®] and treatment was initiated before the age of 18 years.
- This report presents pooled data from both studies, obtained from paediatric patients diagnosed with TS who met the inclusion criteria. Criteria were: GH-naïve at baseline visit, with valid baseline height, age and dosing information, with at least one follow-up visit within a 2-year period.
 - In NordiNet[®] IOS, 'GH-naïve' patients were truly naïve at baseline.
 - In ANSWER, patients could have received GH for up to 6 months prior to baseline.
- A repeated measures mixed model was applied to the data, adjusting for factors previously shown to impact height gain (age at treatment start; baseline and target height standard deviation score).
- Change in height standard deviation score (ΔHSDS) from baseline, and the association between ΔHSDS and average GH dose of <50 or ≥50 µg/kg/day within each year were evaluated at year 1 and year 2.
 - Longitudinal changes were reported as change from baseline for each individual patient.
- This analysis did not evaluate safety outcomes.

Table 2 • Growth hormone exposure for patients with Turner syndrome analysed in this report

	<50 µg/kg/day	≥50 µg/kg/day	All
GH dose at baseline	42.95 (28.57;48.91) n=779	53.55 (50.31;63.73) n=346	46.15 (31.75;55.56) N=1125
Average GH dose during year 1	43.64 (33.34;48.64) n=696	53.53 (50.48;64.62) n=318	46.73 (35.23;56.26) N=1014
Average GH dose during year 2	43.14 (32.01;48.62) n=611	53.80 (50.63;65.27) n=250	46.11 (34.05;56.17) N=861
Average GH dose over years 1 and 2	43.55 (33.03;48.60) n=610	53.64 (50.63;64.98) n=254	46.30 (35.33;55.85) N=864

Data are median (10th;90th percentile) unless otherwise stated. GH, growth hormone.



Results

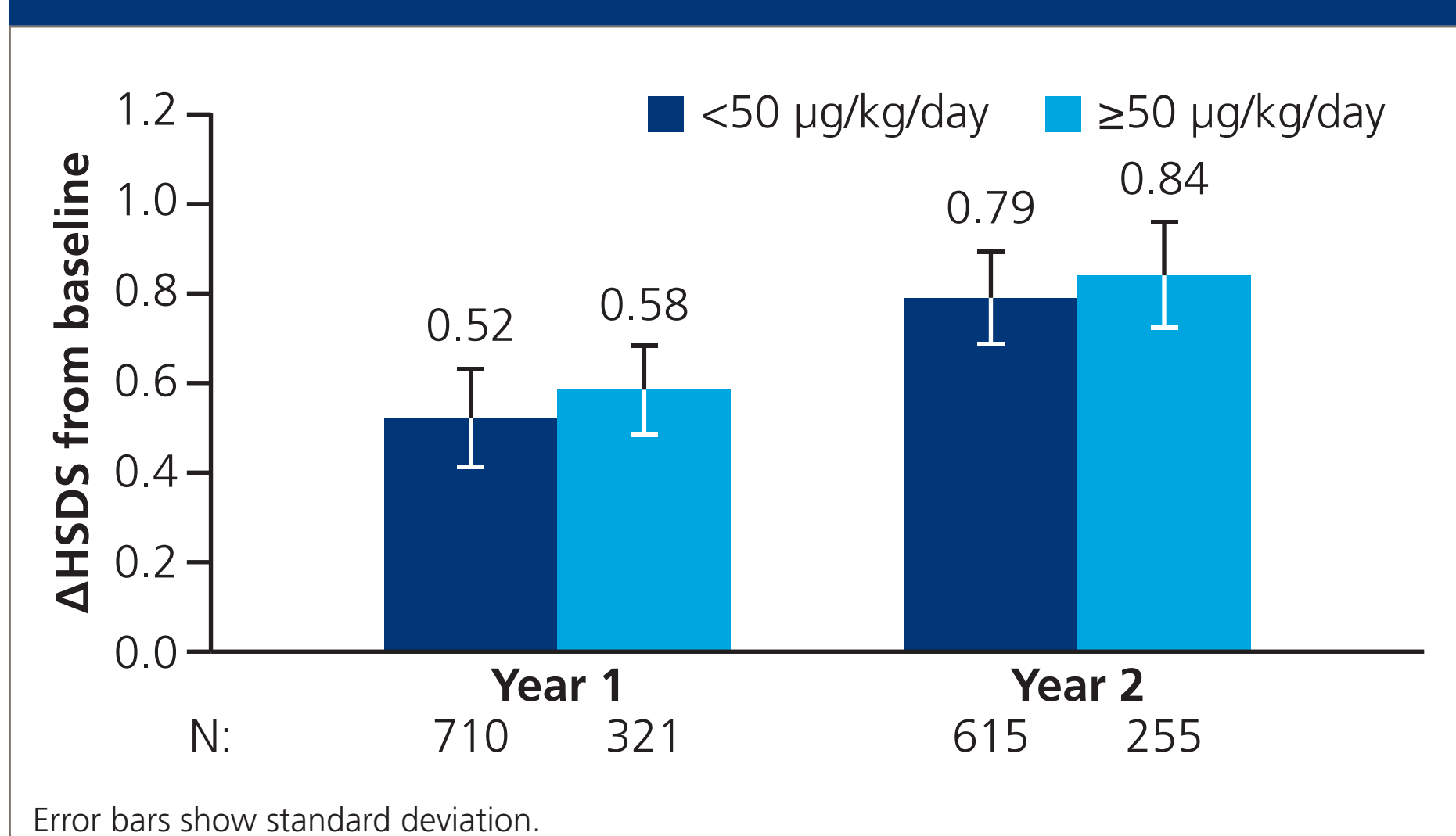
- Of the 38,199 paediatric patients enrolled in both studies, 2409 were diagnosed with TS, and 1125 met the criteria for inclusion in the analysis.
- Baseline characteristics are presented in **Table 1**.
- GH exposure is shown in **Table 2**.
- Mean (standard deviation [SD]) increase in height from baseline (cm) was 8.46 (2.53) (n=1014) at year 1 and 15.12 (3.66) (n=864) at year 2.
- A GH dose of ≥50 µg/kg/day was associated with a significantly greater ΔHSDS than a dose of <50 µg/kg/day (p=0.0407).
- Estimated mean (SD) ΔHSDS from baseline at years 1 and 2, by GH dose group, is shown in **Figure 1**.

Table 1 • Baseline characteristics for patients with Turner syndrome analysed in this report

Patients, n	1125
Age, years (n=1125)	8.60 (3.84)
Height, cm (n=1125)	114.76 (19.7)
Height SDS* (n=1125)	-2.61 (0.92)
Target height SDS (n=1125)	-0.18 (0.97)
IGF-I SDS† (n=623)	-0.84 (1.48)
Bone age/chronological age (n=404)	0.87 (0.15)

Data are presented as mean (SD) unless otherwise stated. *Height SDS were calculated using age- and gender-specific national reference values. †IGF-I SDS was calculated using the Brabant 2003 age- and gender-specific reference values (Brabant G et al. *Horm Res* 2003;60:53–60). IGF-I, insulin-like growth factor-I; SD, standard deviation; SDS, standard deviation score.

Figure 1 • Mean change in height standard deviation score (ΔHSDS) from baseline in years 1 and 2 of follow-up by average growth hormone dose (<50 or ≥50 µg/kg/day)



Error bars show standard deviation.

Conclusions

- Real-world data from NordiNet[®] IOS and the ANSWER Program indicate that patients with TS exhibit dose-dependent, short-term responsiveness to GH therapy.
- GH doses of ≥50 µg/kg/day were associated with greater short-term height gain than lower doses.
- Our data support the concept that dose optimisation during the first 2 years of GH therapy may improve height outcomes in the TS patient population.

References

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Conflict of interest disclosures

JB and TRR are Novo Nordisk consultants and have received speaker honoraria, travel grants and unrestricted research grants from Novo Nordisk. BTP is an employee of, and own stocks/shares in, Novo Nordisk A/S. SR is an employee of Novo Nordisk Health Care AG. PB is a consultant for Novo Nordisk, Ipsen and Novartis. He has received travel compensation and research grants from Novo Nordisk, and research support from Ipsen.

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