P1 - 628

Height Gain and Safety Outcomes in Growth Hormone-Treated Children with Idiopathic Short Stature: Experience from a Prospective Observational Study

Christopher J Child[1]*, Charmian A Quigley[2], Alan G Zimmermann[3], Cheri Deal[4], Judith L Ross[5], Ron G Rosenfeld[6], Gordon B Cutler Jr.[7], Werner F Blum[8]

[1]Lilly Research Laboratories, Eli Lilly and Company, Windlesham, UK; [2]Sydney Children's Hospital, Randwick, Australia; [3]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, USA; [4]University of Montreal and CHU Ste-Justine, Montreal, Canada; [5]Department of Pediatrics, Thomas Jefferson University, Philadelphia, USA; [6]Oregon Health Sciences University, Portland, USA; [7]Cutler Consultancy LLC, Deltaville, USA; [8]University Children's Hospital, University of Giessen, Giessen, Germany. *Presenting Author: Employed by and stockholder of Eli Lilly and Company

1) BACKGROUND AND AIMS

Background

- Idiopathic short stature (ISS) is a diagnosis of exclusion that encompasses many short children referred to pediatric endocrinologists.
- In 2003 the FDA approved growth hormone (GH) treatment for ISS based on data from 2 randomized, controlled clinical trials (1, 2).
- Eligibility for GH treatment in ISS is restricted to children who have baseline (BL) height standard deviation score (HtSDS) ≤-2.25 and are unlikely to attain normal adult height (Ht).

Aims

- To evaluate enrolment, short-term Ht gain, final (adult) height (FHt) and safety outcomes in an ISS cohort treated in routine clinical practice.
- Data collected in GeNeSIS (Genetics and Neuroendocrinology of Short Stature International Study)
  - a prospective, multinational, observational study collecting data on GH-treated (GH-tx) pediatric patients with a broad variety of growth disorders from 1999 to 2015.
  - all GH-treatment decisions were at the discretion of the investigators.

2) PATIENTS AND METHODS

Patients

- Of 22161 patients overall, 2833 GH-tx patients had an investigator-provided diagnosis of ISS.
  - 91% were from the USA, 81% had Caucasian ethnicity and 71% were male (the gender ratio generally remained stable throughout the 1999-2013 enrolment period).
- Two ISS populations were investigated:
  1. GH-tx patients who were naïve to GH treatment at study entry and had HtSDS available at baseline (BL), 1st, 2nd, 3rd and 4th year of treatment (N=420)
  2. GH-tx patients (GH naïve and previously-treated) with BL Ht and FHt available (N=530)
  - FHt was defined by at least 1 of the following: closed epiphyses, Ht velocity <2 cm/year, or last bone age >14 years (girls) or >16 years (boys).

Statistics

- Standard deviation scores (SDS) for Ht and target Ht (mid-parental) were calculated using age- and gender-matched data from the US National Center for Health Statistics (3).
- Statistically significant differences between groups were determined by non-overlap of 95% confidence intervals for effectiveness variables (values not shown, but indicated by *).

3) RESULTS: Demographics, Treatment Characteristics and Height Gain Outcomes

Population 1: Patients with 4 years of GH treatment

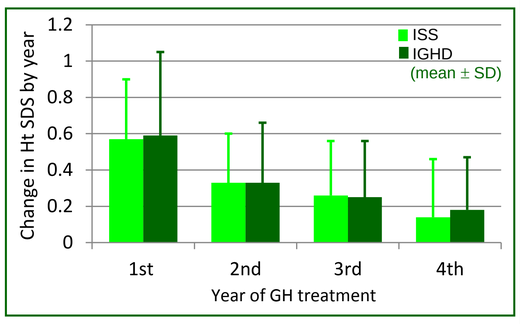
- To place data from patients with ISS in context, corresponding data from patients with idiopathic growth hormone deficiency (IGHD) are shown.
- Patients with ISS were significantly older at BL and received higher GH doses (Table 1).
- Change in Ht SDS at 1, 2, 3, and 4 years were similar in patients with ISS and IGHD (Figure 1)

Table 1: Selected demographics and baseline characteristics in patients with ISS and IGHD

Variable (mean ± SD, unless stated)	**ISS** (N=420[1])	**IGHD** (N=2401[1])
Sex (%)	23 F / 77 M	21 F / 79 M
Age (years)	10.2 ± 2.7*	9.3 ± 3.3*
BMI SDS	-0.8 ± 1.3	-0.6 ± 1.5
Height SDS	-2.4 ± 0.7	-2.5 ± 0.8
Target height SDS	-0.5± 0.7	-0.6 ± 0.8
Initial GH dose (mg/kg/wk)	0.31 ± 0.08*	0.23 ± 0.06*

[1]Maximum N, lower for some variables; * significantly different between groups based on non-overlap of 95% CIs. Abbreviations: BMI = body mass index; CI = confidence interval; F = female; M = male; N = number; SDS = standard deviation score

Figure 1: Change in height SDS at 1, 2, 3 and 4 years in patients with ISS and IGHD



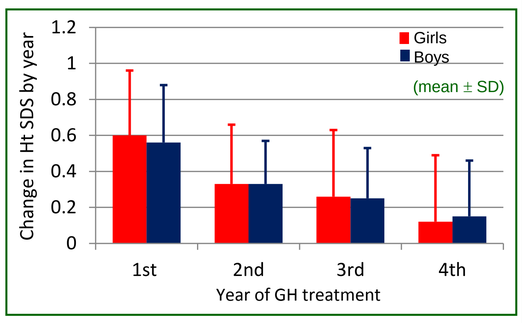
- Girls with ISS were significantly younger and shorter at BL than boys (Table 2) but had comparable change in Ht SDS at 1, 2, 3 and 4 years of GH treatment (Figure 2).

Table 2: Selected demographics and baseline characteristics in girls and boys with ISS

Variable (mean ± SD)	**Girls** (N=108[1])	**Boys** (N=312[1])
Age (years)	9.7 ± 2.3*	10.4 ± 2.8*
BMI SDS	-0.8 ± 1.4	-0.9 ± 1.3
Height SDS	-2.7 ± 0.7*	-2.3 ± 0.6*
Target height SDS	-0.6 ± 0.8	-0.5 ± 0.7
Initial GH dose (mg/kg/wk)	0.30 ± 0.09	0.31 ± 0.07

[1]Maximum N, lower for some variables; * significantly different between groups based on non-overlap of 95% CIs. Abbreviations: BMI = body mass index; CI = confidence interval; F = female; M = male; N = number; SDS = standard deviation score

Figure 2: Change in height SDS at 1, 2, 3 and 4 years in girls and boys with ISS

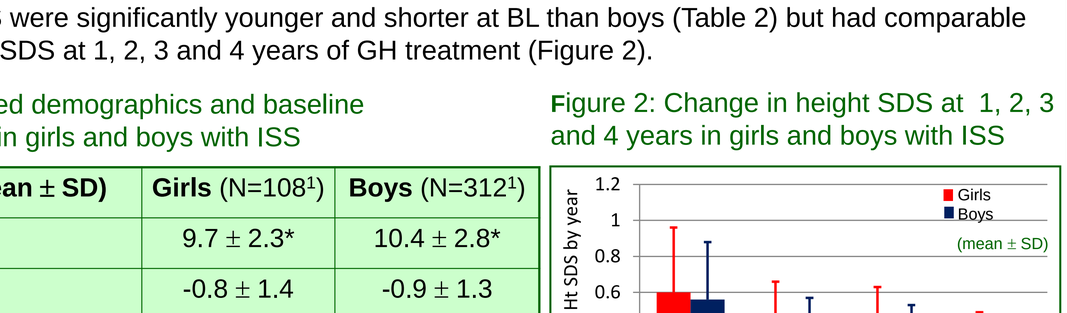


Population 2: Patients who attained final height

- No significant sex differences for Ht SDS, target Ht SDS, BMI SDS or GH dose at BL (data not shown).
- Mean ± SD FHt SDS gain was 1.1 ± 1.0 (all ISS patients, Figure 3a), with 83% achieving FH >-2 SDS.
- FHt SDS and FHt SDS gain were greater for boys than girls, but boys had longer GH therapy duration (Figure 3 c & d).

Figure 3: Final height gain and patient characteristics at final height for patients with ISS and IGHD

[1] Maximum N, lower for some variables
* significantly different between groups based on non-overlap of 95% CIs
Abbreviations:
BL = baseline;
BMI = body mass index;
FHt = final height;
Ht = height;
N = number;
SDS = standard deviation score.



	a) ISS (N=530[1])	**b) IGHD (N=2130[1])**	**c) ISS Girls (N=189[1])**	**d) ISS Boys (N=341[1])**
Age	16.6 ± 1.7 years	16.8 ± 1.9 years	15.5 ± 1.6 years*	17.2 ± 1.4 years*
Change in BMI SDS	0.6 ± 1.0*	0.5 ± 1.2*	0.5 ± 0.9	0.7 ± 1.1
Last GH dose	0.37 ± 0.12 mg/kg/wk*	0.27 ± 0.12 mg/kg/wk*	0.37 ± 0.12 mg/kg/wk	0.36 ± 0.12 mg/kg/wk
GH therapy duration	4.2 ± 2.4 years*	5.2 ± 3.1 years*	3.5 ± 2.1 years*	4.6 ± 2.4 years*

4) RESULTS: Safety Outcomes

Adverse events during GeNeSIS participation

- 2632 patients with ISS had ≥1 follow-up visit and were therefore eligible for assessment of treatment-emergent adverse events (TEAEs).
- Mean duration of follow-up was 2.9 ± 2.1 years.
- To place the TEAE rates in patients with ISS in context, data are also provided for patients with IGHD, those born small for gestational age (SGA) and the composite group of all diagnoses in GeNeSIS.
- Rates of patients with ≥1 TEAE were similar across the diagnostic groups (Table 3).

Table 3: TEAE rates in GH-treated patients with ISS and other diagnoses (specific events at rates ≥1.0%)

	ISS [N (%)][a]	**IGHD [N (%)]**	**SGA [N (%)]**	**All Diagnoses [N (%)]**
N	2632	10276	1164	20769
Patients with no TEAE	2013 (76.5)	8187 (79.7)	814 (69.9)	14785 (72.2)
Patients with ≥1 TEAE	619 (23.5)	2089 (20.3)	350 (30.1)	5984 (28.8)
Headache[b]	72 (2.7)	193 (1.9)	32 (2.8)	573 (2.8)
ADHD[b]	65 (2.5)	132 (1.3)	22 (1.9)	341 (1.6)
Arthralgia[b]	47 (1.8)	135 (1.3)	21 (1.8)	350 (1.7)
Scoliosis[b]	41 (1.6)	124 (1.2)	17 (1.5)	394 (1.9)
Hypothyroidism[b]	32 (1.2)	222 (2.2)	23 (2.0)	588 (2.8)
Precocious puberty[b]	31 (1.2)	78 (0.8)	38 (3.3)	239 (1.2)

Abbreviations: ADHD = attention deficit/hyperactivity disorder; N = number; TEAE = treatment-emergent adverse event.
[a] Events are presented by order of decreasing prevalence in the ISS group.
[b] Total cases of individual TEAE in study population, not by patient.

Specific safety outcomes and events

- The following key outcomes/events were reported for the ISS cohort:
  - 1 death (due to septic meningitis)
  - 1 malignancy (malignant nevus); in addition a case of gonadoblastoma was reported in the streak gonad of a girl with 46,XY mixed gonadal dysgenesis who was originally reported with an ISS diagnosis
  - 3 cases of type 1 diabetes, no cases of type 2 diabetes
  - no cases of stroke.

5) DISCUSSION

- The proportion of GH-tx girls with ISS in GeNeSIS remained substantially lower than that of boys throughout the 14-year enrolment period and did not change following FDA approval in 2003 (4).
- GH-mediated Ht gain in patients with ISS was similar to that seen in other studies (1, 2, 5) and in patients with IGHD.
- No significant difference in change in Ht SDS in years 1 to 4 was observed between GH-tx girls and boys; boys achieved greater FHt SDS gain, but were treated on average for >1 year more than girls.
- Rates of TEAEs in patients with ISS were similar to those observed for IGHD, SGA, and all diagnoses.

6) CONCLUSIONS

- **Data from a large cohort of patients with ISS treated with GH in routine clinical practice demonstrated the following:**
  - **substantial Ht SDS gain from baseline to FHt, equivalent to ~ 7 cm Ht gain**
  - **fewer girls received GH therapy than boys during GeNeSIS, but had similar Ht gain**
  - **no additional safety concerns specific to GH treatment of patients with ISS relative to other short stature diagnoses.**

7) REFERENCES:

1. Leschek EW et al. 2004. Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: A randomized, double-blind, placebo-controlled Trial. *J Clin Endocrinol Metab* 89:3140-3148.
2. Wit JM et al. 2005. Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. *J Pediatr* 146:45-53
3. Ogden CL et al. 2002. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics* 109:45-60.
4. Grimberg A. et al. 2015. Gender bias in U.S. pediatric growth hormone treatment. Sci Rep 5 11099; doi: 10.1038/srep1109..
5. Counts DR et al. 2015. A 4-year, open-label, multicenter, randomized trial of Genotropin® growth hormone in patients with idiopathic short stature: analysis of 4-year data comparing efficacy, efficiency, and safety between an individualized, target-driven regimen and standard dosing. *Horm Res Pediatr* 84:79-87.

Funded by Eli Lilly and Company. European Society for Paediatric Endocrinology 55th Annual Meeting, Paris, 10 –12 September 2016. Thanks to all participating investigators and patients.

55ESPE 628--P1

Growth

Chris Child

DOI: 10.3252/pso.eu.55ESPE.2016

Poster presented at: ESPE 2016 PARIS 10-12 SEPTEMBER

PosterSessionOnline.com