Research

Growth hormone treatment of Canadian children: results from the GeNeSIS phase IV prospective observational study

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Abstract

Background: Country-specific data on outcomes of treatment with recombinant human growth hormone are lacking. We present such data for children treated with growth hormone in Canada.

Methods: We describe characteristics and outcomes of 850 children (mean age at baseline 8.5 yr) treated with growth hormone constituting the Canadian cohort of the multinational phase IV prospective observational Genetics and Neuroendocrinology of Short-stature International Study (GeNeSIS). The diagnosis associated with short stature was as determined by the investigator. Auxological data were evaluated yearly until near-adult height. Adverse events were assessed in all growth-hormone–treated patients.

Results: The diagnosis ascribed as the cause of short stature was growth hormone deficiency in 526 children (61.9%), predominantly organic rather than idiopathic, particularly congenital pituitary abnormalities and intracranial tumours. All diagnostic groups with sufficient patients for analysis had increased height velocity standard deviation score (SDS) and height SDS during growth hormone treatment. For patients who reached near-adult height (n = 293), the mean height SDS was within the normal range for about 80% of patients with organic growth hormone deficiency (n = 131) or idiopathic growth hormone deficiency (n = 50), 50% of patients with idiopathic short stature (n = 10) and 46% of patients with Turner syndrome (n = 79). Eleven deaths were reported, 7 in patients with organic growth hormone deficiency. Serious adverse events considered related to growth hormone treatment (n = 19) were isolated except for medulloblastoma recurrence (n = 2) and adenoidal hypertrophy (n = 2).

Interpretation: Growth hormone treatment was effective and had a good safety profile in Canadian children. Growth hormone dosages were lower than in the US and global GeNeSIS cohorts, and a greater proportion of treated Canadian children had organic growth hormone deficiency. **Study registration:** ClinicalTrials.gov, no. NCT01088412.

Children with short stature and/or growth failure may benefit from growth hormone treatment to increase adult height.[1] Recombinant human growth hormone was initially approved for growth hormone deficiency, which remains the main indication and can be due to congenital or acquired causes.[2,3] Pediatric growth hormone therapy has been approved in many countries for additional conditions, including Turner syndrome, Prader–Willi syndrome, chronic renal insufficiency, short stature homeobox-containing gene (*SHOX*) deficiency, Noonan syndrome and idiopathic short stature, as well as for children born small for gestational age.[1,4–11] For approved indications and dosages, growth hormone therapy is generally believed to be safe.[12–14]

Large observational studies of growth-hormone–treated patients have been used to examine long-term outcomes and safety in "real-world" settings.[15–21] These include the phase IV prospective observational Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS), implemented in 1999, which enrolled over 23 000 patients from 827 sites in 30 countries. Canada has a long history in helping establish growth hormone safety and effectiveness through clinical trials and surveillance programs,[4,22–24] beginning in the 1960s and continuing until 2015 with GeNeSIS. Although

such multinational surveillance studies provide global information, uptake and outcomes of growth hormone treatment across and between countries may be affected by differences in indications and dosages, age chosen for treatment initiation, funding sources for treatment and patient characteristics. Country-specific data on outcomes of growth hormone therapy have been reported to only a limited extent.[19,25–28] The objective of the current report was to evaluate outcomes of growth hormone treatment in pediatric patients in Canada, comparing findings with those from the United States and the overall global population, using data from GeNeSIS.

Methods

Patient population

The multinational phase IV prospective observational study GeNeSIS was designed to examine the safety and effectiveness of growth hormone (Humatrope, Eli Lilly and Company) administered in children with growth disorders.

The observational nature of GeNeSIS meant that all diagnoses and measurements were as reported by and all treatment decisions were at the discretion of the participating investigator. Growth hormone deficiency and idiopathic short stature were defined with the use of current guidelines.[14,29] The definition of short stature is an auxological one, referring to measured height in a child that is –2 standard deviations (SDs) beneath the population mean. Abnormal growth velocity is defined as the crossing of growth centiles in a child or adolescent and therefore requires serial growth measurements, typically 3–6 months apart. Patients were enrolled at 14 centres in Canada. The present report examined data from the start of the study, in April 1999, until study completion, in September 2015.

Study evaluations

The 2000 US National Center for Health Statistics standards[30] were used to calculate height SD score (SDS) for all countries in GeNeSIS except Japan. Prespecified age- and sex-matched reference data[31] were used for height velocity SDS. Target height was based on the sex-adjusted average of parental heights where available; pubertal stage was recorded according to the Tanner classification.[32,33] Near-adult height was defined as the patient's having reached 1 of the following criteria: closed epiphyses, height velocity less than 2 cm/yr, or bone age greater than 14 years for girls or greater than 16 years for boys.

Adverse events were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) version 18.1, with the investigators' assessing the potential relation to growth hormone treatment (possibly/probably or not related). Serious adverse events were classified according to Canadian guidelines.[34] Treatment-emergent adverse events were defined as events that first occurred or worsened in severity after the start of growth hormone treatment and, thus, were evaluated only in those with at least 1 postbaseline visit.

Statistical analysis

The observational nature of the study meant that various data were missing for some patients. Each analysis used the maximum available data, and patient numbers therefore varied between specific analyses. Changes in auxological parameters during treatment were evaluated for the following patient subgroups: 1) growth hormone naive at entry, with both baseline and 1-year height SDS data ($n = 274$), 2) growth hormone naive at entry, with yearly height measurements for at least 4 years ($n = 165$) and 3) reached near-adult height during the study and were either growth hormone naive or already treated with growth hormone at entry to GeNeSIS ($n = 293$). Data are presented as mean with 95% confidence interval (CI) for continuous variables, and as frequency and percentage for categorical variables. Outcomes across different groups could be compared by examination of the overlap of 95% CI. We conducted statistical analyses using SAS 9.1 (SAS Institute).

Ethics approval

Data were collected according to the ethical principles of the Declaration of Helsinki, and the protocol was approved by appropriate local ethics review committees. Written informed consent for data collection, processing and publication was provided by a parent/legal guardian according to national laws and regulations.

Results

Patient characteristics

Data for 848 growth-hormone–treated Canadian children (430 boys [50.7%] and 417 girls [49.2%]; in 1 case [0.1%], the sex was unknown) were evaluable for effectiveness analyses; data for 2 further patients were included only in safety analyses. At GeNeSIS entry, 528 children (62.3%) were already receiving growth hormone, and 320 (37.7%) were growth hormone naive. Ethnic origin was white for 308/342 patients (90.1%) with relevant information; however, ethnicity data were not provided for 508 patients (59.8%). The most frequent primary diagnosis was growth hormone deficiency (526 [61.9%]) (Table 1), reported to be due to organic causes in most cases (379/526 [72.1%]). Of the 379 patients with organic growth hormone deficiency, 184 (48.5%) had congenital pituitary development abnormalities, and 102 (26.9%) had an intracranial tumour. After growth hormone deficiency, the next largest diagnostic category was Turner syndrome (156 [18.4%]). The proportions of children with idiopathic growth hormone deficiency and idiopathic short stature were higher in the US than in Canada, whereas the proportion with Turner syndrome appeared lower in the US (Table 1).

The overall mean age at the start of growth hormone treatment was 8.5 years (range 0.01–18.2 yr). For diagnostic groups most frequently reported (Supplementary Table A1, Appendix 1, available at www.cmajopen.ca/content/6/3/E372/suppl/DC1), the mean age at the start of growth hormone treatment was highest for patients with idiopathic short stature. Patients with organic growth hormone deficiency had a

Table 1: Reported primary diagnosis in children in Canada, the United States and globally treated with growth hormone for short stature*

Primary diagnosis†	No. (%) of children		
	Canada n = 850	United States n = 9806	Globally‡ n = 22 290
Growth hormone deficiency	526 (61.9)	5184 (52.9)	14 036 (63.0)
Idiopathic	147 (17.3)	4088 (41.7)	11 029 (49.5)
Classic	133 (15.6)	3198 (32.6)	9524 (42.7)
Neurosecretory dysfunction	4 (0.5)	533 (5.4)	919 (4.1)
Organic	379 (44.6)	1065 (10.9)	2958 (13.3)
Congenital	243 (28.6)	665 (6.8)	1888 (8.5)
Abnormal pituitary development	184 (21.6)§	522 (5.3)	1431 (6.4)
Clinical syndromes	35 (4.1)¶	57 (0.6)	159 (0.7)
Genetic defect	6 (0.7)	16 (0.2)	131 (0.6)
Other central nervous system malformations	10 (1.2)	53 (0.5)	124 (0.6)
Acquired	136 (16.0)	400 (4.1)	1067 (4.8)
Intracranial tumour	102 (12.0)**	273 (2.8)	786 (3.5)
Cranial irradiation	13 (1.5)††	23 (0.2)	62 (0.3)
Central nervous system injury/infection	2 (0.2)	16 (0.2)	44 (0.2)
Histiocytosis	2 (0.2)	17 (0.2)	35 (0.2)
Other	14 (1.6)	71 (0.7)	137 (0.6)
Other defects of growth hormone axis (e.g., bioinactive growth hormone)	0 (0.0)	31 (0.3)	103 (0.5)
Syndromes associated with short stature homeobox deficiency	162 (19.1)	804 (8.2)	2463 (11.0)
Turner syndrome	156 (18.4)	737 (7.5)	1868 (8.4)
Mixed gonadal dysgenesis	3 (0.4)	6 (0.1)	20 (0.1)
Léri–Weill syndrome	2 (0.2)	21 (0.2)	318 (1.4)
Short stature homeobox deficiency — other	1 (0.1)	40 (0.4)	257 (1.2)
Other causes of short stature or reduced linear growth	61 (7.2)	540 (5.5)	1023 (4.6)
Genetic defect	43 (5.1)	273 (2.8)	481 (2.2)
Other	18 (2.1)‡‡	267 (2.7)	542 (2.4)
Idiopathic short stature	38 (4.5)§§	2594 (26.4)§§	2842 (12.8)§§
Small for gestational age	19 (2.2)	353 (3.6)	1276 (5.7)
Skeletal dysplasia	2 (0.2)	19 (0.2)	68 (0.3)
No growth hormone deficiency¶¶	19 (2.2)	52 (0.5)	99 (0.4)
Prader–Willi syndrome	16 (1.9)	33 (0.3)	64 (0.3)
Other	3 (0.4)	19 (0.2)	35 (0.2)

*Investigator-provided diagnoses were assigned to a predefined hierarchical diagnostic tree to classify the primary cause of short stature and establish appropriate diagnostic groups; however, more detailed levels of diagnosis were not always provided, so number of subdiagnoses may not sum to number of main diagnostic groups in all cases.
†Diagnosis was unknown for 23 children in Canada, 229 in US and 380 globally.
‡Includes Canada and US.
§Includes patients with primary diagnoses of ectopic posterior pituitary (76), septo-optic dysplasia (67), pituitary hypoplasia (18), pituitary aplasia (10) and pituitary stalk defect (8).
¶Includes patients with primary diagnoses of Prader–Willi syndrome (30; reported as a diagnosis associated with growth hormone deficiency), midline palatial defect (3) and other (2).
**Includes patients with primary diagnoses of medulloblastoma (43), craniopharyngioma (26), glioma (9), astrocytoma (7), germinoma (4), primitive neuroectodermal (2), ependymoma (1), pituitary adenoma (1) and unspecified (9).
††Treatment for leukemia (12) and medulloblastoma (1).
‡‡Includes patients with primary diagnoses of Noonan syndrome (4), chronic renal failure (2), glucocorticoid therapy (2), rheumatoid arthritis (1), inflammatory bowel disease (1) and other — unspecified (8).
§§Includes children with primary diagnoses of constitutional delay of growth and familial short stature (Canada 7, US 43, globally 93).
¶¶A small number of patients indicated as not having growth hormone deficiency by the investigator were enrolled with complex diagnoses that, following the structure of the diagnostic module on the case report form, would routinely be recorded under growth hormone deficiency; assignment of no growth hormone deficiency status to these patients means that, in general, their data were not included in efficacy analyses of the main study diagnostic groups but were included in safety-related analyses.

lower mean age at the start of treatment than did patients with idiopathic growth hormone deficiency. Age at the start of treatment was 10 years or more for 47.5% (*n* = 180) of patients with organic growth hormone deficiency, 64.6% (*n* = 95) of those with idiopathic growth hormone deficiency, 57.1% (*n* = 89) of those with Turner syndrome and 78.9% (*n* = 30) of those with idiopathic short stature. At baseline, most patients (278/324 girls [85.8%] and 234/293 boys [79.9%]) were prepubertal, with similar proportions across diagnostic groups except for idiopathic short stature (40.0% [*n* = 2/5] and 48.0% [*n* = 12/25], respectively).

The mean peak growth hormone level in growth hormone stimulation tests was less than 5 μg/L for both patients with

organic growth hormone deficiency and those with idiopathic growth hormone deficiency, versus 24.1 μg/L for those with idiopathic short stature. Stimulated peak growth hormone levels in Canadian children with growth hormone deficiency were lower than those in the global cohort (Supplementary Table A1, Appendix 1). The mean dosage at the start of growth hormone treatment was highest for patients with Turner syndrome (0.29 [95% CI 0.28 to 0.29] mg/kg per wk) and lowest for patients with organic growth hormone deficiency (0.18 [95% CI 0.18 to 0.19] mg/kg per wk). Canadian mean growth hormone dosages were lower than those in the US (data not shown) or global cohorts. The reported mean duration of growth hormone treatment was 6.6 (95% CI 6.3 to 6.9) years

Table 2 (part 1 of 2): Patient characteristics and auxological data at baseline and after 1 year of growth hormone treatment for patients naive to growth hormone treatment at study entry and with baseline and 1-year height measurements available, by primary diagnostic category*

Characteristic	Diagnostic category; mean (95% CI)†				
	Organic growth hormone deficiency	Idiopathic growth hormone deficiency	Turner syndrome	Idiopathic short stature	Small for gestational age
Canada	*n* = 89	*n* = 57	*n* = 44	*n* = 25	*n* = 5
Baseline					
Male sex, no. (%)	54 (61)	38 (67)	–	21 (84)	4 (80)
Age, yr	8.9 (7.8 to 10.0)	11.3 (10.2 to 12.4)	9.6 (8.5 to 10.6)	12.9 (11.8 to 14.0)	6.3 (3.7 to 9.0)
Height SDS	−1.87 (−2.13 to −1.60)	−2.58 (−2.91 to −2.25)	−2.76 (−2.97 to −2.55)	−2.57 (−2.96 to −2.18)	−4.02 (−5.40 to −2.65)
Height velocity, cm/yr	5.17 (4.12 to 6.22)	4.22 (3.39 to 5.04)	4.96 (4.24 to 5.67)	4.58 (3.78 to 5.37)	6.32 (3.15 to 9.49)
Height velocity SDS	−1.65 (−2.05 to −1.24)	−1.55 (−2.04 to −1.05)	−1.01 (−1.54 to −0.47)	−0.61 (−1.58 to 0.35)	0.31 (−4.70 to 5.32)
Target height SDS	0.25 (0.03 to 0.47)	−0.37 (−0.64 to −0.10)	0.18 (−0.04 to 0.40)	−0.44 (−0.72 to −0.15)	−0.62 (−1.26 to 0.03)
Target height SDS deficit‡	−2.19 (−2.54 to −1.84)	−2.22 (−2.62 to −1.83)	−2.92 (−3.18 to −2.66)	−2.13 (−2.55 to −1.72)	−3.41 (−5.16 to −1.65)
Stimulated peak growth hormone level, μg/L	4.3 (2.4 to 6.1)	4.4 (3.6 to 5.3)	NA	25.0 (17.2 to 32.8)	NA
Growth hormone dosage, mg/kg per wk	0.18 (0.17 to 0.19)	0.18 (0.17 to 0.19)	0.29 (0.28 to 0.30)	0.22 (0.19 to 0.25)	0.22 (0.15 to 0.29)
Year 1					
Height SDS	−1.30 (−1.54 to −1.05)	−1.97 (−2.29 to −1.65)	−2.28 (−2.54 to −2.03)	−2.24 (−2.64 to −1.83)	−3.45 (−4.75 to −2.15)
Height velocity, cm/yr	9.30 (8.28 to 10.33)	8.79 (8.14 to 9.44)	7.84 (7.28 to 8.40)	7.31 (6.33 to 8.28)	7.24 (5.59 to 8.90)
Height velocity SDS	1.72 (1.31 to 2.13)	2.20 (1.58 to 2.81)	2.54 (1.54 to 3.53)	1.47 (0.76 to 2.17)	1.49 (−0.12 to 3.10)
Height SDS gain	0.59 (0.43 to 0.76)	0.60 (0.46 to 0.73)	0.50 (0.38 to 0.61)	0.33 (0.21 to 0.45)	0.57 (0.14 to 1.00)
Target height SDS deficit‡	−1.60 (−1.93 to −1.27)	−1.61 (−1.99 to −1.24)	−2.44 (−2.72 to −2.16)	−1.80 (−2.23 to −1.36)	−2.83 (−4.46 to −1.20)
Growth hormone dosage, mg/kg per wk	0.19 (0.18 to 0.20)	0.19 (0.18 to 0.20)	0.30 (0.29 to 0.31)	0.24 (0.21 to 0.27)	0.27 (0.21 to 0.33)

overall and was longest for patients with organic growth hormone deficiency (8.0 yr, 95% CI 7.5 to 8.4 yr) and shortest for those with idiopathic short stature (2.7 yr, 95% CI 2.2 to 3.2 yr; not all data shown). The duration of growth hormone treatment was more than 4 years for 556 patients (65.4%).

Height data during growth hormone therapy
Auxological data at baseline and at 1 year for patients naive to growth hormone treatment at study entry are summarized in Table 2 for Canada and the global database. For Canadian patients overall, the mean height velocity SDS increased from –1.19 (95% CI –1.43 to –0.94) at baseline to 1.97 (95% CI 1.69 to 2.26) at 1 year. All diagnostic groups had a mean gain in height SDS at 1 year, with the least gain in those with idiopathic short stature (0.33 [95% CI 0.21 to 0.45]) and the greatest gain in patients with idiopathic growth hormone deficiency (0.60 [95% CI 0.46 to 0.73]).

Table 2 (part 2 of 2): Patient characteristics and auxological data at baseline and after 1 year of growth hormone treatment for patients naive to growth hormone treatment at study entry and with baseline and 1-year height measurements available, by primary diagnostic category*

Characteristic	Diagnostic category; mean (95% CI)†				
	Organic growth hormone deficiency	Idiopathic growth hormone deficiency	Turner syndrome	Idiopathic short stature	Small for gestational age
All countries combined (including Canada)	*n* = 1210	*n* = 5974	*n* = 886	*n* = 1353	*n* = 756
Baseline					
Male sex, no. (%)	766 (63.3)	3988 (66.8)	–	967 (71.5)	405 (53.6)
Age, yr	8.8 (8.5 to 9.1)	10.3 (10.2 to 10.4)	9.2 (9.0 to 9.4)	11.5 (11.3 to 11.6)	8.6 (8.3 to 8.8)
Height SDS	–2.42 (–2.50 to –2.34)	–2.39 (–2.41 to –2.37)	–2.56 (–2.62 to –2.50)	–2.36 (–2.40 to –2.32)	–2.62 (–2.68 to –2.56)
Height velocity, cm/yr	4.54 (4.32 to 4.75)	4.70 (4.64 to 4.77)	4.86 (4.66 to 5.06)	4.81 (4.65 to 4.96)	5.22 (5.02 to 5.41)
Height velocity SDS	–1.56 (–1.70 to –1.42)	–0.99 (–1.04 to –0.93)	–1.11 (–1.26 to –0.96)	–0.72 (–0.84 to –0.60)	–0.84 (–0.99 to –0.69)
Target height SDS	–0.06 (–0.11 to 0.00)	–0.55 (–0.57 to –0.53)	0.07 (0.01 to 0.13)	–0.54 (–0.59 to –0.50)	–0.64 (–0.70 to –0.58)
Target height SDS deficit‡	–2.42 (–2.50 to –2.33)	–1.84 (–1.86 to –1.81)	–2.62 (–2.69 to –2.55)	–1.82 (–1.87 to –1.76)	–1.98 (–2.07 to –1.90)
Stimulated peak growth hormone level, µg/L	4.5 (4.1 to 4.8)	8.2 (8.0 to 8.4)	N/A	16.9 (16.3 to 17.4)	14.1 (13.1 to 15.1)
Growth hormone dosage, mg/kg per wk	0.22 (0.21 to 0.22)	0.23 (0.23 to 0.24)	0.31 (0.31 to 0.32)	0.32 (0.32 to 0.33)	0.27 (0.27 to 0.28)
Year 1					
Height SDS	–1.65 (–1.72 to –1.58)	–1.85 (–1.87 to –1.83)	–2.10 (–2.16 to –2.04)	–1.87 (–1.91 to –1.82)	–2.05 (–2.11 to –2.00)
Height velocity, cm/yr	9.76 (9.54 to 9.98)	8.79 (8.73 to 8.85)	7.83 (7.70 to 7.97)	8.63 (8.51 to 8.76)	8.52 (8.37 to 8.68)
Height velocity SDS	3.21 (3.02 to 3.40)	2.48 (2.42 to 2.54)	2.26 (2.07 to 2.45)	2.38 (2.26 to 2.50)	2.34 (2.19 to 2.49)
Height SDS gain	0.78 (0.74 to 0.82)	0.56 (0.55 to 0.57)	0.48 (0.46 to 0.51)	0.52 (0.50 to 0.54)	0.58 (0.55 to 0.61)
Target height SDS deficit‡	–1.63 (–1.70 to –1.55)	–1.29 (–1.32 to –1.27)	–2.16 (–2.23 to –2.09)	–1.31 (–1.37 to –1.26)	–1.41 (–1.49 to –1.33)
Growth hormone dosage, mg/kg per wk	0.23 (0.22 to 0.23)	0.25 (0.25 to 0.25)	0.32 (0.32 to 0.33)	0.35 (0.35 to 0.36)	0.29 (0.29 to 0.30)

Note: CI = confidence interval, NA = data available for less than 60% of patients, SDS = standard deviation score.
*Patient numbers are for those with height SDS at baseline and 1 year, but not all patients had all other information.
†Except where noted otherwise.
‡Height SDS minus target height SDS.

Mean height SDS and height velocity SDS over the first 4 years of growth hormone treatment are shown in Figure 1. For each diagnostic group, mean height velocity SDS increased in the first year and declined over subsequent years.

Auxological parameters for all patients who reached near-adult height are shown in Table 3, and mean gain in height SDS is shown in Figure 2. Near-adult height SDS was greater than –2.0 for most Canadian patients with organic growth hormone deficiency and idiopathic growth hormone deficiency but for only about half of those with Turner syndrome or idiopathic short stature. Mean age at baseline was lower and mean therapy duration to near-adult height was longer for patients with organic growth hormone deficiency than for those with idiopathic growth hormone deficiency; however, this did not result in a greater mean change from baseline for height SDS (Figure 2).

Safety outcomes

Of the 850 Canadian children included in the safety analysis (Table 4), 11 died during the study period; patient characteristics and cause of death are shown in Supplementary Table A2, Appendix 1. Seven patients with organic growth hormone deficiency died. Death was considered possibly related to growth hormone treatment by the investigator for 3 of these patients, for whom the primary diagnosis was medulloblastoma ($n = 2$) or anaplastic astrocytoma ($n = 1$); the cause of death was tumour recurrence in each case.

Serious adverse events were reported for 97 patients, with events in 19 patients (2.2%; see Table 4 footnote) considered by the investigator to be related to growth hormone treatment. The treatment-related serious adverse events were single events in individual patients
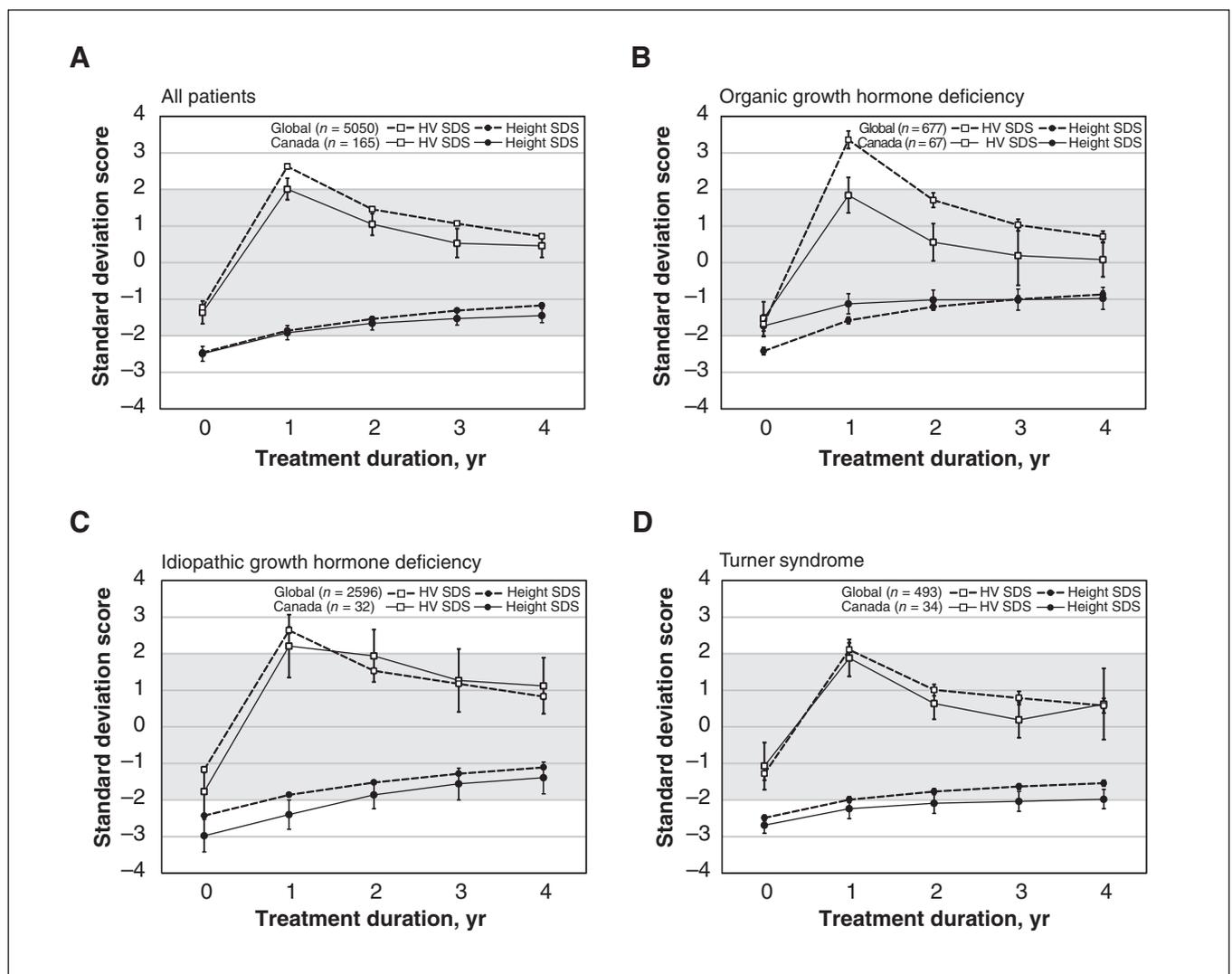

Figure 1: Mean height velocity standard deviation score (HV SDS) and height SDS over the first 4 years of growth hormone treatment for patients in Canada and the global population with data for each year who were naive to growth hormone treatment at study entry, for all patients ([A]) and for evaluable diagnostic groups ([B], [C] and [D]). Standard deviation score corresponds to the following height percentiles on a standard height-for-age growth curve: –3 SDS = 0.2%, –2 SDS = 2.3%, –1 SDS = 16.0%, 0 SDS = 50.0%, 1 SDS = 86.0%, 2 SDS = 97.7%, 3 SDS = 99.8%. Data for patients with idiopathic short stature are not shown because of the small number of patients ($n = 9$) in this diagnostic group in Canada with relevant data. Grey shading delineates "normal" values within ± 2 SDs. Error bars = 95% confidence intervals.

Table 3 (part 1 of 2): Characteristics and auxological data at baseline and at near-adult height for patients with idiopathic growth hormone deficiency, organic growth hormone deficiency or Turner syndrome who were growth hormone treated or growth hormone naive at study entry

Characteristic	Diagnostic category; mean (95% CI)*				
	All patients	Organic growth hormone deficiency	Idiopathic growth hormone deficiency	Turner syndrome	Idiopathic short stature
Canada	*n* = 293	*n* = 131	*n* = 50	*n* = 79	*n* = 10
Baseline					
Male sex, no. (%)	147 (50.2)	89 (67.9)	33 (66.0)	–	9 (90.0)
Age, yr	10.2 (9.8 to 10.6)	9.2 (8.5 to 9.9)	11.4 (10.4 to 12.5)	10.3 (9.8 to 10.9)	12.8 (11.3 to 14.4)
Height SDS	−2.62 (−2.78 to −2.46)	−2.29 (−2.57 to −2.00)	−2.70 (−3.06 to −2.33)	−2.99 (−3.15 to −2.83)	−2.52 (−3.25 to −1.79)
Target height SDS deficit†	−2.51 (−2.69 to −2.32)	−2.32 (−2.62 to −2.02)	−2.14 (−2.56 to −1.71)	−2.91 (−3.11 to −2.71)	−1.81 (−2.61 to −1.01)
Height velocity SDS	−1.49 (−1.71 to −1.27)	−1.89 (−2.23 to −1.54)	−1.29 (−1.75 to −0.83)	−1.16 (−1.44 to −0.89)	−0.25 (−1.32 to 0.83)
Growth hormone dosage, mg/kg per wk	0.22 (0.21 to 0.23)	0.18 (0.17 to 0.18)	0.20 (0.17 to 0.23)	0.29 (0.28 to 0.29)	0.24 (0.18 to 0.30)
Stimulated peak growth hormone level, µg/L	4.73 (3.99 to 5.47)	2.90 (2.48 to 3.32)	4.15 (3.36 to 4.94)	NA	19.41 (14.65 to 24.18)
Near-adult height					
Age, yr	17.8 (17.6 to 17.9)	18.1 (17.8 to 18.3)	17.6 (17.1 to 18.1)	17.6 (17.3 to 17.9)	17.2 (15.6 to 18.9)
Height SDS	−1.42 (−1.56 to −1.27)	−0.95 (−1.15 to −0.75)	−1.07 (−1.38 to −0.76)	−2.04 (−2.24 to −1.83)	−2.02 (−2.89 to −1.14)
Near-adult height SDS less baseline height SDS	1.17 (1.01 to 1.33)	1.26 (0.98 to 1.54)	1.63 (1.27 to 1.99)	0.96 (0.78 to 1.13)	0.50 (−0.35 to 1.35)
Target height SDS deficit†	−1.28 (−1.44 to −1.13)	−0.93 (−1.15 to −0.71)	−0.52 (−0.80 to −0.24)	−1.94 (−2.16 to −1.72)	−1.31 (−2.29 to −0.32)
Growth hormone therapy duration, yr	6.46 (6.01 to 6.90)	7.68 (6.93 to 8.44)	5.45 (4.48 to 6.42)	5.71 (5.18 to 6.25)	3.19 (1.97 to 4.42)
Last growth hormone dosage, mg/kg per wk	0.22 (0.21 to 0.23)	0.17 (0.16 to 0.18)	0.20 (0.19 to 0.22)	0.29 (0.28 to 0.30)	0.24 (0.18 to 0.30)
Near-adult height SDS > −2.0, no. (%)	66	79	80	46	50

except for the aforementioned 2 medulloblastoma recurrences and adenoidal hypertrophy in 2 patients.

Of the 833 patients with at least 1 postbaseline visit, 587 (70.5%) had at least 1 treatment-emergent adverse event reported (Table 4). Treatment-emergent adverse events were reported more frequently among patients with organic growth hormone deficiency than among those with idiopathic growth hormone deficiency or other diagnoses. The most frequently reported treatment-emergent adverse events for Canadian patients overall were headache and secondary hypothyroidism, consistent with the known growth hormone safety profile and inherent risk of hypothyroidism owing to the underlying diagnosis. Treatment-emergent adverse events classified by the investigator as possibly related to growth hormone treatment occurred in 87 patients (10.2%).

Interpretation

The results of GeNeSIS indicated a positive treatment effect on height gain, both during the first 1–4 years of growth hormone therapy and at near-adult height, and a reassuring safety profile both within Canada and globally. Of the 30 countries involved in GeNeSIS, Canada was the sixth-largest contributor of patients, with 850 growth-hormone–treated patients (3.9%) out of roughly 22 000 globally. Currently approved pediatric indications in Canada are growth hormone deficiency (approved in 1987), Turner syndrome (1997), small for gestational age (2006), idiopathic short stature (2006) and *SHOX* deficiency (2008); chronic renal insufficiency is an approved indication for some growth hormone formulations (1996) but not for the growth hormone primarily used in GeNeSIS.

Table 3 (part 2 of 2): Characteristics and auxological data at baseline and at near-adult height for patients with idiopathic growth hormone deficiency, organic growth hormone deficiency or Turner syndrome who were growth hormone treated or growth hormone naive at study entry

Characteristic	Diagnostic category; mean (95% CI)*				
	All patients	Organic growth hormone deficiency	Idiopathic growth hormone deficiency	Turner syndrome	Idiopathic short stature
All countries combined (including Canada)	*n* = 5076	*n* = 754	*n* = 2322	*n* = 695	*n* = 552
Baseline					
Male sex, no. (%)	2576 (50.7)	448 (59.4)	1412 (60.8)	–	360 (65.2)
Age, yr	10.9 (10.8 to 11.0)	9.8 (9.5 to 10.1)	11.2 (11.1 to 11.3)	10.0 (9.8 to 10.3)	12.3 (12.0 to 12.5)
Height SDS	−2.42 (−2.45 to −2.40)	−2.27 (−2.38 to −2.17)	−2.38 (−2.41 to −2.34)	−2.65 (−2.71 to −2.58)	−2.37 (−2.43 to −2.30)
Target height SDS deficit†	−2.02 (−2.06 to −1.99)	−2.29 (−2.40 to −2.17)	−1.80 (−1.85 to −1.76)	−2.69 (−2.77 to −2.61)	−1.74 (−1.83 to −1.65)
Height velocity SDS	−1.01 (−1.07 to −0.95)	−1.51 (−1.69 to −1.33)	−0.98 (−1.06 to −0.89)	−1.04 (−1.22 to −0.87)	−0.63 (−0.80 to −0.47)
Growth hormone dosage, mg/kg per wk	0.27 (0.26 to 0.27)	0.22 (0.21 to 0.22)	0.25 (0.24 to 0.25)	0.32 (0.31 to 0.32)	0.33 (0.32 to 0.34)
Stimulated peak growth hormone level, μg/L	9.46 (9.18 to 9.74)	4.18 (3.80 to 4.55)	8.26 (7.95 to 8.57)	14.06 (12.50 to 15.61)	16.49 (15.51 to 17.47)
Near-adult height					
Age, yr	17.3 (17.2 to 17.3)	18.0 (17.8 to 18.2)	17.2 (17.1 to 17.3)	17.1 (16.9 to 17.3)	17.2 (17.0 to 17.4)
Height SDS	−1.18 (−1.21 to −1.15)	−0.80 (−0.90 to −0.69)	−1.01 (−1.05 to −0.97)	−1.70 (−1.77 to −1.63)	−1.26 (−1.34 to −1.18)
Near-adult height SDS less baseline height SDS	1.24 (1.21 to 1.27)	1.46 (1.35 to 1.58)	1.37 (1.33 to 1.41)	0.95 (0.89 to 1.01)	1.10 (1.02 to 1.19)
Target height SDS deficit†	−0.76 (−0.79 to −0.77)	−0.73 (−0.83 to −0.62)	−0.43 (−0.47 to −0.39)	−1.74 (−1.81 to −1.66)	−0.60 (−0.70 to −0.51)
Growth hormone therapy duration, yr	5.82 (5.72 to 5.91)	7.59 (7.26 to 7.91)	5.51 (5.37 to 5.64)	6.38 (6.12 to 6.63)	4.67 (4.44 to 4.91)
Last growth hormone dosage, mg/kg per wk	0.28 (0.28 to 0.28)	0.20 (0.19 to 0.21)	0.27 (0.26 to 0.27)	0.32 (0.31 to 0.33)	0.36 (0.35 to 0.37)
Near-adult height SDS > −2.0, no. (%)	81	84	86	66	82

Note: CI = confidence interval, NA = data available for less than 60% of patients, SDS = standard deviation score.
*Except where noted otherwise.
†Height SDS minus target height SDS.

The majority of patients (61.9% in Canada, 63.0% globally and 52.9% in the US) had growth hormone deficiency. However, the proportions with organic growth hormone deficiency (44.6%, 13.3% and 10.9%, respectively) versus idiopathic growth hormone deficiency (17.3%, 49.5% and 41.7%, respectively) reflected a higher frequency of inclusion in Canada of patients with abnormal pituitary development and intracranial tumour. The proportion of patients with Turner syndrome was also higher in Canada than in the global and US cohorts (18.4%, 8.5% and 7.5%, respectively), which may, in part, have been attributable to enrolment in GeNeSIS of patients from a large Canadian clinical trial.[4] In addition, fewer patients in Canada than in the US had idiopathic short stature or were born small for gestational age. This likely indicates a more conservative approach of endocrine specialists in Canada to administering growth hormone to children with conditions not due to growth hormone deficiency, with the exception of Turner syndrome. Also, treatment of children with idiopathic short stature and those born small for gestational age is privately funded in many provinces in Canada, whereas growth hormone deficiency is fully reimbursed by provincial health insurance programs.

Patients showed increased height velocity SDS within the first year, with a positive mean value maintained over the first
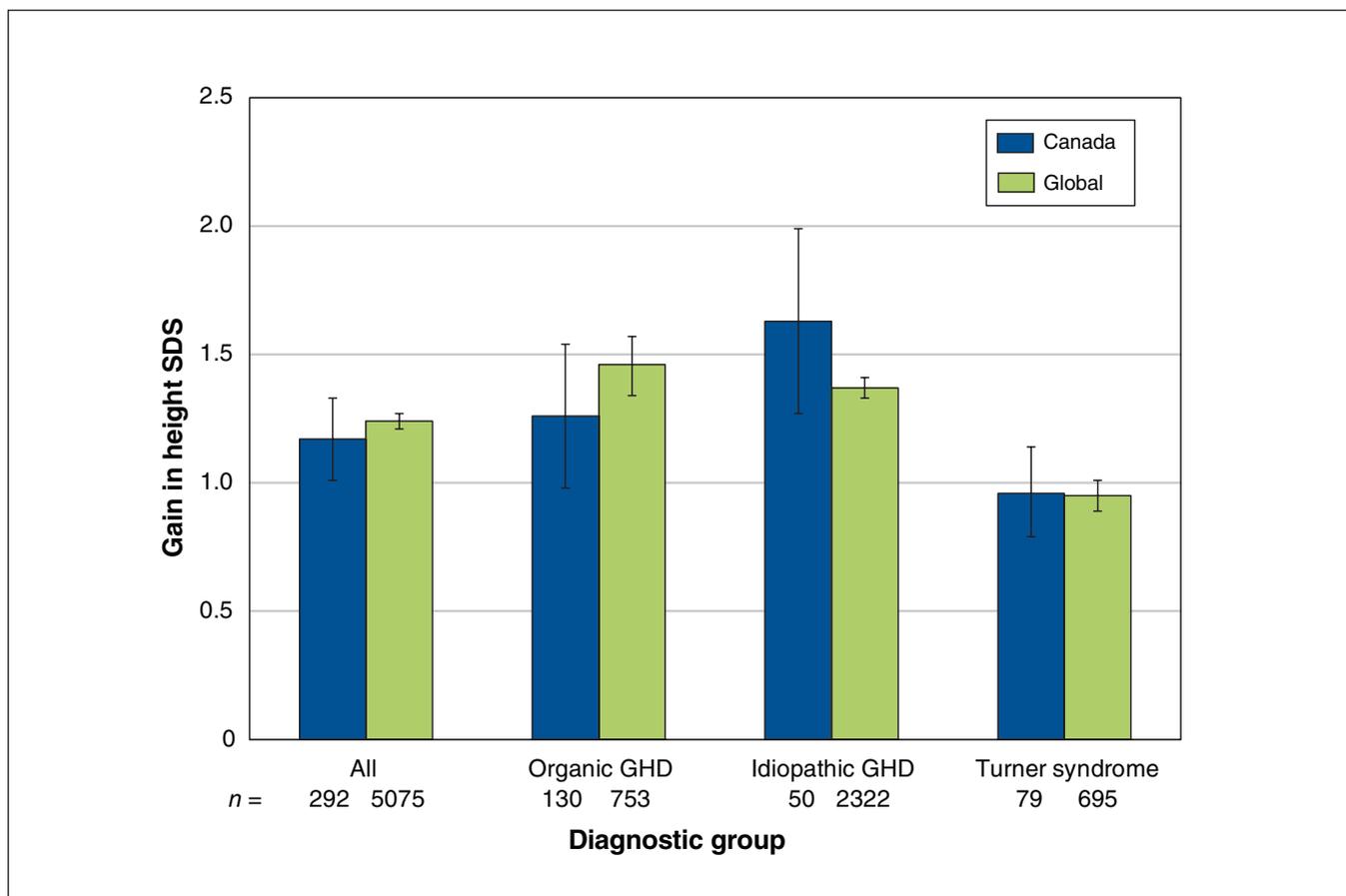
Figure 2: Change in height standard deviation score (SDS) from baseline to near-adult height for all growth-hormone–treated patients and by diagnostic group in Canada and the global population. Data for patients with idiopathic short stature are not shown because of the small number of patients (*n* = 10) in this diagnostic group in Canada with relevant data. Error bars = 95% confidence intervals. Note: GHD = growth hormone deficiency.

3–4 years of growth hormone treatment, resulting in an increase in height SDS over time. Across all indications, growth response in the Canadian cohort was lower than that seen in the global cohort. Potential explanations for the differences in growth hormone response include the more conservative approach to treatment dosages in Canada than in the global, and particularly the US, populations, and the inclusion of milder or transient forms of growth hormone deficiency in the global cohort compared to a more severely affected group of patients in Canada.

Canadian patients with Turner syndrome were shorter than the global cohort at near-adult height, and proportions with near-adult height SDS within the normal range were lower than global proportions. This finding is consistent with past research showing near-adult height to be influenced by age at the start of growth hormone treatment, growth hormone dosage and concomitant estrogen treatment.[6,35–37] However, patients with Turner syndrome in Canada had a similar gain in height SDS from baseline to near-adult height as the global cohort, at 0.96. This gain was consistent with the results from the Canadian randomized clinical trial and other studies of growth hormone treatment in Turner syndrome.[4,5,38] The tendency of Canadian physicians to treat

shorter patients with Turner syndrome may reflect parent/patient health care priorities,[37] although the impact of provincial funding decisions may also play a role.

Treatment-emergent adverse events were reported more frequently among Canadian patients than among the global population (70.5% v. 30.1%), which suggests that physicians in Canada may be more vigilant in reporting adverse events than physicians in other countries. Indeed, the Canadian cohort was the second-largest contributor of adverse events to the global database, surpassed only by the Netherlands, a country with an established national registry. With a mean treatment duration of 6.6 years, 11 (1.3%) of the 850 Canadian patients were reported to have died (standardized mortality ratio 3.0 [95% CI 1.5 to 5.4]). This was a higher frequency of death than that reported among the 21 106 patients in the global cohort with follow-up in study and known sex, who were treated for a mean of 5.0 years (42 deaths [0.2%]).[21] The Canadian cohort included a higher proportion of patients with organic growth hormone deficiency (particularly with a history of intracranial tumour) than the global cohort. Of the 11 reported deaths, 7 were of children with a primary diagnosis of organic growth hormone deficiency; 4 of the 7 died because of cancer recurrence, and 1 patient previously treated

Table 4: Serious and treatment-emergent adverse events reported in Canada

Adverse event	Diagnostic category; no. (%) of patients who reported adverse event					
	All patients	Organic growth hormone deficiency	Idiopathic growth hormone deficiency	Turner syndrome	Idiopathic short stature	Small for gestational age
All patients	n = 850	n = 379	n = 147	n = 156	n = 38	n = 19
Death*	11 (1.3)	7 (1.8)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Considered related to growth hormone treatment†	2 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse event	97 (11.4)	61 (16.1)	7 (4.8)	9 (5.8)	3 (7.9)	1 (5.3)
Considered related to growth hormone treatment‡	19 (2.2)	12 (3.2)	1 (0.7)	4 (2.6)	2 (5.3)	0 (0.0)
Patients with ≥ 1 follow-up visit	n = 833	n = 377	n = 137	n = 153	n = 38	n = 19
≥ 1 treatment-emergent adverse event§	587 (70.5)	299 (79.3)	72 (52.6)	108 (70.6)	21 (55.3)	13 (68.4)
Headache	88 (10.6)	55 (14.6)	12 (8.8)	9 (5.9)	2 (5.3)	3 (15.8)
Secondary hypothyroidism	60 (7.2)	45 (11.9)	6 (4.4)	1 (0.6)	0 (0.0)	0 (0.0)
Scoliosis	54 (6.5)	22 (5.8)	10 (7.3)	12 (7.8)	0 (0.0)	3 (15.8)
Ovarian failure	50 (6.0)	9 (2.4)	0 (0.0)	41 (26.8)	0 (0.0)	0 (0.0)
Arthralgia	48 (5.8)	16 (4.2)	5 (3.6)	13 (8.5)	1 (2.6)	1 (5.3)
Upper respiratory tract infection	44 (5.3)	31 (8.2)	5 (3.6)	6 (3.9)	0 (0.0)	1 (5.3)
Hypothyroidism	42 (5.0)	29 (7.7)	4 (2.9)	8 (5.2)	0 (0.0)	0 (0.0)
Adverse event considered related to growth hormone treatment¶	87 (10.4)	48 (12.7)	6 (4.4)	18 (11.8)	3 (7.9)	2 (10.5)
Headache	19 (2.3)	16 (4.2)	0 (0.0)	2 (1.3)	0 (0.0)	1 (5.3)
Scoliosis	10 (1.2)	9 (2.4)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Arthralgia	9 (1.1)	4 (1.1)	0 (0.0)	3 (2.0)	0 (0.0)	0 (0.0)
Increase in insulin-like growth factor level	9 (1.1)	0 (0.0)	0 (0.0)	5 (3.3)	0 (0.0)	1 (5.3)
Melanocytic nevus	7 (0.8)	4 (1.1)	0 (0.0)	3 (2.0)	0 (0.0)	0 (0.0)
Otitis media	6 (0.7)	4 (1.1)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)

*See Supplementary Table A2, Appendix 1 for details.
†Both due to recurrence of medulloblastoma.
‡All serious adverse events considered related to growth hormone treatment occurred in single patients except for medulloblastoma recurrence in 2 patients (both with organic growth hormone deficiency) and adenoidal hypertrophy in 2 patients (1 with organic growth hormone deficiency, 1 with Turner syndrome). Other serious adverse events reported as related to growth hormone treatment were meningioma, neoplasm progression, aortic valve incompetence, rectal hemorrhage, edema, death, parotitis, upper limb fracture, type 1 diabetes mellitus, optic glioma, anaplastic astrocytoma, adrenal neoplasm, increased intracranial pressure, ischemic stroke, tonsillar hypertrophy, sleep apnea syndrome, scoliosis surgery, meningioma surgery, adenoidectomy and angiodysplasia; some patients experienced more than 1 event.
§Any treatment-emergent adverse event irrespective of relatedness with frequency of 5% or more among all patients.
¶Any treatment-emergent adverse event considered related with frequency greater than 0.5% among all patients.

with cranial irradiation died because of a second cancer. Analyses from various studies have indicated an increased risk of death in patients previously treated for malignant disease, irrespective of growth hormone treatment.[21,39–42] Results from the Childhood Cancer Survivor Study indicate no association of death or tumour recurrence with growth hormone treatment,[42] which supports the assessment that these deaths were unlikely to be related to growth hormone treatment. Nevertheless, 3 of the deaths (2 recurrences of medulloblastoma and 1 anaplastic astrocytoma recurrence) were recorded by the investigators as being possibly related to growth hormone treatment; many investigators are cautious in assessing such events in the absence of defining factors and may state that a relation to growth hormone treatment cannot be ruled out, whereas others may reject the possibility of a causal relation based on temporal association or risk factors.

A previous analysis of GeNeSIS showed no increased risk for primary cancers during study participation in patients with no previous cancer history compared to general population cancer registries.[16] Similarly, the US Pediatric Endocrine Society Drug and Therapeutics Committee found no association between growth hormone treatment and the risk of de novo cancer development in children with no prior history of or known predisposition to cancer.[43]

Analyses from the large Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) cohort showed an increased risk of death from several second malignant disorders in patients whose original diagnosis was cancer,[44] with no clear raised risk in patients with growth failure without other major disease. Initial reports from the Childhood Cancer Survivor Study indicated that growth hormone treatment was associated with a higher relative risk for second neoplasms.[39,45] However, a more recent analysis of that study, with an extended period of follow-up, showed no direct evidence to support an increased risk of second neoplasms of the central nervous system in growth-hormone–treated patients, who clearly have risk factors other than growth hormone for development of subsequent neoplasms.[42] Our observational study cannot resolve this question, but the balance of evidence suggests that the risk of malignant disease relates to the underlying condition rather than to growth hormone treatment.

Limitations

This analysis of Canadian data from GeNeSIS is limited in that the study was open-label and observational; however, the data reflect the real-world clinical setting of growth hormone treatment for a large patient cohort. In addition, biases are possible because of missing or incorrect reporting of data.

Conclusion

This study of growth-hormone–treated Canadian children, followed in an observational setting, showed that the major indication for growth hormone treatment in Canada is organic growth hormone deficiency. Overall effectiveness and safety results were generally consistent with those from other clinical trials and international surveillance databases. About 80% of patients with organic growth hormone deficiency or idiopathic growth hormone deficiency achieved a near-adult height within the normal range despite use of a lower dosage of growth hormone than that used in the global GeNeSIS population; smaller proportions of children with conditions not due to growth hormone deficiency achieved near-adult height within the normal range. The 11 reported deaths generally reflected the serious underlying cause of growth hormone deficiency. Although the current approach to growth hormone treatment in Canada is more conservative than some other global practices, it appears efficacious and safe. However — as per international guidelines[13] — continued monitoring of patients previously treated with growth hormone is recommended.

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