Clinical Research Article

Long-Term Safety of Growth Hormone Treatment in Childhood: Two Large Observational Studies: NordiNet IOS and ANSWER

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Abbreviations: ADR, adverse drug reaction; AE, adverse event; ANSWER, American Norditropin Studies: Web-Enabled Research; GH, growth hormone; GHD, growth hormone deficiency; ICP, intracranial pressure; NordiNet IOS, NordiNet International Outcome Study; SADR, serious adverse drug reaction; SAGhE, Safety and Appropriateness of Growth hormone treatments in Europe; SCFE, slipped capital femoral epiphysis; SGA, small for gestational age; SOC, system organ class.

Abstract

Context: Growth hormone (GH) treatment has a generally good safety profile; however, concerns about increased mortality risk in adulthood have been raised.

Objective: This work aims to assess the long-term safety of GH treatment in clinical practice.

Methods: Data were collected from 676 clinics participating in 2 multicenter longitudinal observational studies: the NordiNet International Outcome Study (2006-2016, Europe) and ANSWER Program (2002-2016, USA). Pediatric patients treated with GH were classified into 3 risk groups based on diagnosis. Intervention consisted of daily GH treatment, and main outcome measures included incidence rates (events/1000 patient-years) of adverse drug reactions (ADRs), serious adverse events (SAEs), and serious ADRs, and their relationship to GH dose.

Results: The combined studies comprised 37 702 patients (68.4% in low-risk, 27.5% in intermediate-risk, and 4.1% in high-risk groups) and 130 476 patient-years of exposure. The low-risk group included children born small for gestational age (SGA; 20.7%) and

non-SGA children (eg, with GH deficiency; 79.3%). Average GH dose up to the first adverse event (AE) decreased with increasing risk category. Patients without AEs received higher average GH doses than patients with more than one AE across all groups. A significant inverse relationship with GH dose was shown for ADR and SAE incidence rates in the low-risk group ($P = .003$ and $P = .001$, respectively) and the non-SGA subgroup (both $P = .002$), and for SAEs in the intermediate- and high-risk groups ($P = .002$ and $P = .05$, respectively).

Conclusions: We observed no indication of increased mortality risk nor AE incidence related to GH dose in any risk group. A short visual summary of our work is available (1).

Key Words: adverse events, childhood, human growth hormone, long-term safety, neoplasms and malignancies, SAGhE

Treatment with recombinant human growth hormone (GH) is used widely in children with growth failure to improve linear growth and with the aim of achieving normal adult height. Treatment with GH has been approved for a variety of indications, including GH deficiency (GHD), short stature in children born small for gestational age (SGA), chronic kidney disease, Turner syndrome, Noonan syndrome, and Prader-Willi syndrome. In the United States, it has also been approved for idiopathic short stature.

Long-term effectiveness and safety of GH treatment in clinical practice has been demonstrated in several longitudinal observational studies (2-11). However, concerns were raised following the preliminary French retrospective study "Safety and Appropriateness of Growth hormone treatments in Europe" (SAGhE) regarding an increase in adult mortality following GH treatment in childhood, in patients categorized a priori into a low-mortality risk group (n = 6928) (12). The risk appeared the highest in patients who received GH doses greater than 50 μg/kg/day, for whom the incidence of bone tumors and cerebral hemorrhage increased (12, 13). In another preliminary SAGhE study from Belgium, the Netherlands, and Sweden, in the low-risk group (n = 2543) the majority of deaths (76%; 16/21) were caused by accidents and suicides, and patients did not die of cardiovascular disease or cancer (14). Lastly, in a recent report from the full SAGhE consortium (Belgium, France, Germany, Italy, the Netherlands, Sweden, Switzerland, and the United Kingdom), with up to 25 years of follow-up and 24 232 patients categorized into 3 risk groups, it was reported that, while some cause-specific mortality from circulatory and hematological diseases was increased in all groups, the mortality was not associated with GH doses in any risk group (15).

We address the long-term safety of GH treatment in pediatric patients by evaluating data from 2 complementary noninterventional studies with a common design: the NordiNet International Outcome Study (IOS) and the American Norditropin Studies: Web-Enabled Research (ANSWER) Program. Interim results from NordiNet IOS have previously been published, after evaluating safety data from 13 834 patients categorized into groups by mortality risk and stratified by average GH dose (16). No safety signals were observed, and no association between GH dose and the incidence of adverse events (AEs) was found (16).

In this paper, we report a combined analysis from the NordiNet IOS and the ANSWER Program, evaluating the entire safety data set from more than 37 000 patients from 23 countries, with up to 10 years of follow-up (17). We evaluated the frequency and incidence rates of serious (SAEs) and/or treatment-related AEs reported during GH treatment in pediatric patients enrolled in the NordiNet IOS and ANSWER Program, who were classified into 3 risk groups based on their diagnosis as per the SAGhE cohort study categorization. We also investigated the effect of GH dose on the incidence rates of AEs and report details on events of special medical interest.

Materials and Methods

Study Design and Ethics

The NordiNet IOS (NCT00960128) and ANSWER Program (NCT01009905) were noninterventional, multicenter registry studies monitoring the long-term outcomes of GH treatment (with Norditropin; Novo Nordisk A/S) in children and adults, in real-world clinical practice. The NordiNet IOS was ongoing between April 2006 and December 2016 and involved 469 clinics in 22 countries throughout Europe and the Middle East; the ANSWER Program took place from June 2002 to September 2016 in 207 clinics in the United States. The designs of both studies have previously been reported in detail (17, 18).

The 2 studies were complementary, with similar aims and using the same data management electronic platform.

Minor differences in study design have been described elsewhere (17). Both studies were conducted with approval from relevant ethics committees, written consent from patients, and pseudonymization of all data in accordance with the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practices, and regulatory requirements.

Patient Population

The patient population analyzed in this study included children with GHD, Turner syndrome, Noonan syndrome, Prader-Willi syndrome, idiopathic short stature, or those born SGA, who were treated with GH as prescribed by the treating physician. Patients were classified into 1 of 3 main risk categories based on clinical diagnosis at the start of GH treatment and associated risk for long-term mortality (irrespective of GH treatment), as described previously (12, 15) and summarized in Table 1. If a patient had several diagnoses, categorization was based on the diagnosis belonging to the highest risk group. Patient classification into risk groups was carried out by the study sponsor and reviewed by 2 pediatric endocrinologists (authors L.S. and J.R.).

Safety Evaluation

Safety was evaluated on the basis of AEs reported by the treating physicians. Events reported prior to the GH treatment start were excluded from the analysis, as well as AEs reported after age 20 years.

Events evaluated in this analysis included (i) SAEs, (ii) AEs considered possibly/probably related to GH treatment, either by the reporting physician or the study sponsor (adverse drug reactions; ADRs), and (iii) serious ADRs (SADRs). Nonserious and non–GH-related AEs were not included in this analysis, in line with the publication of interim data from the NordiNet IOS (16). AEs were considered serious if they resulted in death, a life-threatening experience, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or were associated with a congenital anomaly/birth defect, or important medical events.

An overlap exists between the reported types of AEs. SADRs are a subset of SAEs that are considered related to GH treatment. Similarly, SADRs form a subgroup of ADRs, as ADRs include all nonserious and serious AEs related to GH treatment. Therefore, the total number of events reported in this analysis is the sum of SAEs and ADRs minus the number of SADRs.

All ADRs, SAEs, and SADRs were coded with the Medical Dictionary for Regulatory Activities terms (version 14.0) using system organ class (SOC) terminology. Incidence of events by SOC is reported for preferred-term events that occurred more than 10 times. Exceptions reported in more detail are (i) events of special interest, including neoplasms and cardiovascular events, and (ii) targeted AEs that occurred in previous studies, such as slipped capital femoral epiphysis (SCFE), increased intracranial pressure (ICP; diagnosed by lumbar puncture, computed tomography, or magnetic resonance imaging), edema, and headache (6, 8, 19-21).

Statistical Analysis

All code for statistical analyses was written using the SAS 9.4 software. Baseline and exposure data were summarized using descriptive statistics. The overall duration of GH treatment was calculated for each patient in patient-years of exposure, from the date of first treatment to the

Table 1. Diagnoses at start of growth hormone treatment used for classification of patients into risk groups

1. Low-risk group	2. Intermediate-risk group	3. High-risk group
A. Non-SGA subgroup	Multiple pituitary hormone deficiency	All malignancies
		Langerhans cell histiocytosis
Isolated GHD	Severe cerebral malformation	After bone marrow or solid transplantation
Idiopathic short stature	Short stature and severe extracerebral malformation	Chronic renal failure
Isolated GHD with a minor craniofacial malformation (eg, cleft lip)	Chromosomal anomalies, including Turner syndrome	Syndromes with known increased risk for malignancies (eg, Bloom, Fanconi, Down, and chromosomal breakage syndromes)
	Clinically defined syndromes	Previously treated for cancer
	Severe chronic pediatric disease	
B. SGA subgroup	Long-term steroid use in chronic inflammatory disease	Craniopharyngioma
Short stature in children born SGA	Benign pituitary tumors	
	Cushing disease	

Abbreviations: GHD, growth hormone deficiency; SGA, small for gestational age.

end of the treatment or the patient's last visit. The average GH dose up to the onset of the first AE was used instead of the average GH dose throughout the whole treatment period, for a more accurate analysis of the relationship between AEs and the GH dose. However, for a GH dose comparison between patient groups that did or did not experience AEs, the average GH dose throughout the treatment period was used for patients who did not experience any AEs. This comparison was carried out using the *t* test, and the Satterthwaite approximation was used in the case of inequality of variances (22). Statistically significant differences in all analyses were defined as a *P* value lower than .05.

In each risk group and low-risk subgroup, patients were stratified into 3 GH dose groups based on their average GH dose up to the first AE: 0 to 30, greater than 30 to 40, and greater than 40 µg/kg/day. Unlike the previous analysis of the NordiNet IOS (16), patients in dose groups 0 to 20 and greater than 20 to 30 µg/kg/day were pooled together because of the relatively low numbers of patients treated with a GH dose below 20 µg/kg/day.

Incidence rates of ADRs, SAEs, and SADRs were calculated as the number of events within the study period per 1000 patient-years of exposure for each risk group and each GH dose group. The incidence rates were compared among the risk groups and between the low-risk subgroups by Poisson regression (log-linear model). The relationship between average GH dose up to the first AE and the occurrence of ADRs, SAEs, and SADRs was analyzed using Poisson regression (log-linear model) with the mean GH dose up to the first AE as a continuous explanatory variable.

The incidence of AEs by the duration of follow-up was studied by calculating the proportion of patients experiencing a given type of AE, in a given year, out of all patients exposed that year for the first 5 years of follow-up. The correlation between AE incidence and duration of GH treatment was analyzed with the Spearman rank-order correlation.

Results

Patient Characteristics

In total, 37 702 patients received GH treatment during 130 476 patient-years of exposure. There were 9873 (26.2%) previously GH treated (nonnaive) children and 27 740 (73.8%) GH-naive children (Table 2). Of the 89 remaining patients with an undetermined history of GH treatment, only 1 had reported an AE.

The majority of patients (25 790; 68.4%) were classified into the low-risk group, while 10 369 (27.5%) and

Table 2. Baseline characteristics by risk group

Risk group	Patients in group, n (% of total)	Sex, male/female, %	Age at GH treatment start, y	GH-naive at study inclusion, n (%)	Height SDS at baseline	IGF-1 SDS at baseline	Target height SDS (CDC)	Duration of GH treatment, y
Low risk	25 790 (68.4)	69.5/30.5	10.1 (3.8)	19 562 (76.0)	−2.3 (1.0)	−1.2 (1.7)	−0.7 (1.0)	3.2 (2.6)
Intermediate risk	10 369 (27.5)	48.5/51.5	8.4 (4.5)	7097 (68.6)	−2.5 (1.3)	−1.3 (1.9)	−0.4 (1.0)	4.2 (3.2)
High risk	1543 (4.1)	59.5/40.5	10.3 (3.8)	1081 (70.3)	−2.0 (1.4)	−1.9 (2.1)	−0.2 (1.0)	3.7 (2.8)
All	37 702 (100.0)	63.3/36.7	9.7 (4.0)	27 740 (73.8)	−2.3 (1.1)	−1.2 (1.8)	−0.6 (1.0)	3.5 (2.8)
Low-risk subgroups								
Non-SGA	20 448 (79.3% of low-risk group)	72.7/27.3	10.6 (3.7)	NA	−2.2 (1.0)	−1.3 (1.7)	−0.6 (1.0)	3.0 (2.5)
SGA	5342 (20.7% of low-risk group)	57.4/42.6	8.2 (3.5)	NA	−2.7 (0.9)	−0.7 (1.6)	−0.9 (0.9)	3.7 (2.9)

Abbreviations: AE, adverse event; CDC, US Centers for Disease Control and Prevention; GH, growth hormone; IGF-1, insulin-like growth factor-1; NA, not available; SDS, SD score; SGA, small for gestational age.

1543 (4.1%) were classified into the intermediate-risk and high-risk groups, respectively. Within the low-risk group, 20 488 patients were classified as non-SGA and 5342 as SGA (79.3% and 20.7% of the low-risk group, respectively).

General baseline characteristics of the patients have been published elsewhere (17). Baseline characteristics of patients grouped by risk category are summarized in Table 2. Overall, there were more boys than girls (63.3% vs 36.7%, respectively). The average age at treatment start was 9.7 years and average treatment duration 3.5 years. The intermediate-risk group was the only group with a majority of girls (51.5%). However, without patients with Turner syndrome (n = 2402; 23.2% of the intermediate-risk group), the sex ratio in the intermediate-risk group was 63.1% boys and 36.9% girls. Patients in the intermediate-risk group were on average younger at the start of treatment (8.4 years), with a lower baseline height SD score (SDS; –2.5) and longer duration of GH treatment (4.2 years) compared with the low- and high-risk groups.

Within the low-risk subgroups, on average, children born SGA started treatment earlier (age 8.2 years) with a lower height SDS (–2.7) and were treated for a longer period (3.7 years) than the non-SGA patients (age 10.6 years, height SDS –2.2 and treatment duration 3.0 years).

Growth Hormone Dose up to First Adverse Event

Average and cumulative absolute GH doses and duration of GH treatment up to the onset of the first AE are summarized for each risk group in Table 3. The average GH dose prior to the first AE was significantly higher in the low-risk group than in the intermediate-risk group ($P = .013$), and the dose both in the low- and intermediate-risk groups was significantly higher compared with that in the high-risk group ($P < .001$ for both). The average GH dose prior to the first AE did not differ significantly between the low-risk subgroups. Duration of GH treatment up to the first AE onset was longer in the intermediate-risk group (2.9 years) and similar in the low- and high-risk groups (2.4-2.5 years). Cumulative absolute dose prior to the first AE was higher in the low- and intermediate-risk groups (579-584 mg) compared with the high-risk group (543 mg) (see Table 3).

In the low-risk subgroups, GH dosing between the non-SGA and SGA patients appeared similar; however, non-SGA patients received a higher cumulative absolute GH dose compared with the SGA group.

Almost half of all patients (49.8%) received an average GH dose of more than 40 µg/kg/day up to the first AE. The largest proportion of patients receiving such a dose was in the low-risk group (54.3% of patients), particularly in the non-SGA subgroup (57.4% of the low-risk group). Only 28.6% of patients in the high-risk group received GH doses of more than 40 µg/kg/day (Table 4). The proportion of patients receiving a GH dose of 30 to 40 µg/kg/day before the first AE onset was similar across all risk groups (28.7%-31.5%); however, this dose range was more prevalent in the SGA subgroup (45.5%) compared with the non-SGA subgroup (27.8% of the low-risk group) (see Table 4).

The average GH dose in patients who did not experience any AEs, compared with patients who experienced at least one AE, appeared higher in all 3 risk groups (Fig. 1A) and in the low-risk subgroups (Fig. 1B). This difference was significant in the low-risk group ($P < .001$), intermediate-risk group ($P = .007$) and in the non-SGA low-risk subgroup ($P < .001$).

Frequency and Incidence Rates of Adverse Events

During the 2 studies, 849 patients (2.3%) experienced 1242 AEs (Table 5). Among the risk groups, proportionally more patients experienced AEs in the high-risk group (107; 6.9% of the group) and the intermediate-risk group (361; 3.5%), compared with the low-risk group (381; 1.5%). Within the low-risk group, a slightly higher proportion of the SGA patients experienced AEs (93; 1.7%) compared with the non-SGA patients (288; 1.4%). Among the types of AEs, ADRs were most prevalent in the low-risk group (particularly in the non-SGA subgroup, in which they represented 81.4% of events). SAEs occurred most frequently in the high-risk group (70% of events). SADRs comprised 190 (15.3%) of all events and occurred at a similar rate across all groups.

Incidence rates (events per 1000 patient-years within the study period) were the lowest in the low-risk group (4.7 for ADRs, 2.3 for SAEs, and 0.9 for SADRs) and increased with each higher risk category (7.2 for ADRs, 8.1 for SAEs, and 2.1 for SADRs in the intermediate-risk group, and 13.9 for ADRs, 20.5 for SAEs, and 5.0 for SADRs in the high-risk group). These differences were statistically significant among all risk groups for all 3 event types ($P < .0001$ for all comparisons; Fig. 2A). For the low-risk subgroups, the incidence rate of ADRs was significantly higher in the non-SGA patients ($P = .05$), whereas the incidence rate of SAEs was significantly higher in the SGA subgroup ($P = 0.001$) (Fig. 3A). The incidence rate of SADRs was not significantly different between these subgroups ($P = .472$).

The incidence rates of ADRs, SAEs, and SADRs were also compared in subgroups of patients stratified into GH dose categories, based on average GH dose prior to the first AE onset. The patient distribution into GH dose groups is summarized in Table 4. When evaluating the mean GH

Table 3. Growth hormone dose up to first adverse event

Risk group	Patients in group, n	Patients with AE, n (% of group)	Average GH dose prior to first AE, μg/kg/d	GH dose at onset of AE, μg/kg/d	Duration of GH treatment up to first AE, y	Cumulative absolute dose up to first AE, mg[a]
Low risk	25 790	381 (1.5)	38.7 (11.0)	38.6 (11.8)	2.4 (2.3)	579 (56-2043)
Intermediate risk	10 369	361 (3.5)	36.6 (12.4)	36.2 (12.9)	2.9 (2.8)	584 (52-2189)
High risk	1543	107 (6.9)	31.0 (10.8)	30.8 (11.2)	2.5 (2.2)	543 (64-2139)
Low-risk subgroups						
Non-SGA	20 448	288 (1.4)	38.4 (11.0)	38.5 (11.9)	2.3 (2.2)	588 (52-2066)
SGA	5342	93 (1.7)	39.9 (11.1)	39.0 (11.4)	2.6 (2.5)	541 (59-2009)

Data are reported as mean (SD) unless otherwise specified.

Abbreviations: AE, adverse event; GH, growth hormone; SGA, small for gestational age.

[a]Data are reported as median (10th-90th percentile).

dose up to the first AE as a continuous variable, a significant inverse relationship with GH dose was shown for incidence rates of ADRs and SAEs in the low-risk group ($P = .003$ and $P = .001$, respectively) and for SAEs in the intermediate- and high-risk group ($P = .002$ and $P = .048$, respectively) (Fig. 2B). Within the low-risk group, an inverse relationship with GH dose was found for incidence rates of ADRs and SAEs in the non-SGA subgroup (both $P = .002$) (Fig. 3B).

Analysis of the annual incidence of AEs has shown that the proportion of patients experiencing ADRs, SAEs, and SADRs among all exposed patients remained relatively stable throughout 5 years of follow-up (0.3%-0.6% for ADRs, 0.2%-0.3% for SAEs, and 0.0%-0.1% for SADRs; Fig. 4). There was a significant negative correlation between the occurrence of ADRs and the duration of GH treatment ($P = .037$), whereas it was not significant for SAEs and SADRs ($P = .624$ and $P = .188$, respectively).

Safety Profile

Adverse events by system organ class and preferred term
ADRs were most frequent among "nervous system disorders" (236 events), "musculoskeletal and connective tissue disorders" (228 events), and "general disorders and administration-site conditions" (104 events) (Fig. 5). The most common preferred-term ADRs were headache (205 events), arthralgia (92 events), scoliosis (42 events), and injection-site reaction (26 events).

SAEs were most frequent in "nervous system disorders" (123 events), "musculoskeletal and connective tissue disorders" (70 events), and "infections and infestations" (68 events) (see Fig. 5). The most common preferred-term SAEs were seizure (44 events), and SCFE and scoliosis (20 events each). Of the total 656 SAEs, 15 had a fatal outcome, details of which have been described previously (17). Among the low-risk subgroups, children born SGA were more likely to experience SAEs (1.0% of patients in the subgroup) than non-SGA children (0.2% of patients in the subgroup). This difference was most pronounced in "respiratory, thoracic, and mediastinal disorders" (7.7% vs 0.8% of events in SGA and non-SGA groups, respectively) and "skin and subcutaneous tissue disorders" (7.7% vs 1.6% of events). In non-SGA children, SAEs were more often reported in "psychiatric disorders" (9.0% vs 0.0% of events in non-SGA and SGA groups, respectively) and "musculoskeletal and connective tissue disorders" (17.2% vs 4.6% of events).

SADRs were overall most frequent in "musculoskeletal and connective tissue disorders" (47 events) and "nervous system disorders" (36 events) (see Fig. 5). The most

Table 4. Number of patients and patient-years in growth hormone dose groups within each risk group and low-risk subgroups

Risk group	GH dose group, µg/kg/d	Patients, n (% of risk group)	Patient-years
Low risk	0-30	3617 (14.2)	13 571
	30-40	8000 (31.5)	28 799
	> 40	13 793 (54.3)	38 240
Intermediate risk	0-30	2773 (27.1)	13 187
	30-40	3167 (31.0)	13 708
	> 40	4280 (41.9)	16 140
High risk	0-30	650 (42.8)	2811
	30-40	435 (28.6)	1658
	> 40	434 (28.6)	1231
Low-risk subgroups			
Non-SGA	0-30	2983 (14.8)	11 391
	30-40	5597 (27.8)	19 266
	> 40	11 553 (57.4)	30 424
SGA	0-30	634 (12.0)	2179
	30-40	2403 (45.5)	9533
	> 40	2240 (42.4)	7815

Abbreviations: GH, growth hormone; SGA, small for gestational age.

common preferred-term SADRs were SCFE (18 events), headache, and increased ICP (12 events each).

Vascular events in the low-risk group

There were 2 cardiovascular events in 2 individual patients, both of whom made a recovery. One non-SGA patient experienced hypotension, an SAE considered possibly related to GH treatment. It occurred after 3.5 years of GH treatment with an average dose of 41.5 µg/kg/day. One SGA patient reported a hematoma on the left thigh (not serious and possibly GH-related) after 8.1 years of GH treatment with an average dose of 35.8 µg/kg/day. There were no cases of cerebral hemorrhage in any risk group.

Neoplasms

At baseline, 281 patients (2.7%) in the intermediate-risk group and 868 patients (56.3%) in the high-risk group had a medical history of a neoplasm before GH treatment initiation. Over the course of the study, 56 patients reported 62 neoplasms, of which 37 (59.7%) were considered unlikely related to GH treatment, 22 (35.5%) were possibly GH related, and 3 (4.8%) were probably GH related. Details about the diagnoses and GH treatment of these 56 patients are summarized in Table S1 in the Supplementary Material (23).

Eight neoplasms in 8 patients (0.03%) were reported in the low-risk group. Two of them (0.04%) occurred in the SGA subgroup (benign oral neoplasm possibly GH related, and T-cell lymphoma unlikely GH related), and 6 (0.03%) in the non-SGA subgroup (nephroblastoma and Langerhans cell histiocytosis unlikely to be GH related,

benign juvenile melanoma and malignant mixed mesenchymal tumor possibly GH related, and melanocytic nevus and lipoma probably GH related). None of these patients had a prior history of a neoplasm.

In the intermediate-risk group, 22 neoplasms were reported in 21 patients (0.20%), of which 14 were unlikely to be related to GH treatment, 7 possibly, and 1 probably GH related. Six of these patients had history of a neoplasm before starting GH treatment.

There were 32 neoplasms in 27 patients (1.75%) in the high-risk group, of which 20 were considered unlikely to be related to GH treatment and 12 possibly related. Of the 27 patients, 25 had a history of a malignancy prior to GH treatment initiation. Four events had a fatal outcome (recurrent medulloblastoma unlikely to be related, primitive neuroectodermal tumor unlikely to be related, metastases to meninges possibly related, and acute myeloid leukemia unlikely to be related to the GH treatment). A single case of bone cancer (osteosarcoma in the occipital region) occurred in a 10-year-old girl after 5 years of GH treatment indicated for GHD, with an average dose of 38.6 µg/kg/day. The patient had a history of medulloblastoma diagnosed before the start of GH treatment. After the diagnosis of osteosarcoma, GH treatment was discontinued and the event was considered unlikely related to the treatment.

Targeted adverse events

There were 18 events both of edema and increased ICP, 21 events of SCFE, and 207 events of headache. Edema was the most common in the intermediate-risk group (12/18 events;

2.1% of all AEs in the risk group), whereas headache and increased ICP were the most common in the low-risk group (106/207 [21.3%] and 10/18 [2.0%], respectively). SCFE occurrence was the highest in the high-risk group (4/21 events; 2.4% of all AEs in the group). Among the low-risk subgroups, the occurrence of edema and increased ICP was higher in the non-SGA children compared with those SGA

Figure 1. Comparison of average growth hormone dose between patients who did or did not experience at least one adverse event in A, risk groups and B, low-risk subgroups. Only significant *P* values (< .05) are shown. For patients with AEs, average GH dose up to the first AE onset was used. For patients without AEs, average GH dose from the full treatment period was used. AE, adverse event; GH, growth hormone; SGA, small for gestational age.

(5/5 and 8/10 events, respectively [1.3% and 2.1% of all AEs in the subgroup, respectively]). Headache occurred at a similar rate in both subgroups (81/207 [21.5%] in the non-SGA and 25/207 [20.7%] in the SGA subgroup), as well as SCFE (6/8 [1.6%] in the non-SGA and 2/8 [1.7%] in the SGA subgroup).

Patients experiencing any of the 4 targeted AEs received a higher mean GH dose at the AE onset (38.9-43.7 μg/kg/day) compared with the whole patient population (30.8-38.6 μg/kg/day). The average duration of GH treatment up to the AE onset was shorter in patients experiencing increased ICP and edema (1.5 and 1.8 years, respectively) and similar for SCFE and headache (2.7 and 2.4 years, respectively), compared with the whole population for any AE (2.4-2.9 years). Diagnoses of the patients experiencing these targeted events, together with information about the duration of GH treatment and GH dose, are summarized in Table S2 in the Supplementary Material (23).

Discussion

This analysis of 2 large, noninterventional, real-world studies, the NordiNet IOS and ANSWER Program, provides valuable insight into the safety of GH treatment with 5-year follow-up in clinical practice. No unexpected safety signals were observed, and the safety profile of GH treatment in this analysis was consistent with other observational studies reported previously (8, 24-26), including our preliminary analysis of data from the NordiNet IOS (16).

Analyses presented in this report were based on patients categorized into 3 risk groups to overcome the complication of analyzing a highly heterogeneous cohort with different preexisting risks. Indeed, we observed that the AE incidence rates within the study period correlated with increasing risk category for all 3 types of AE (Fig. 2A), as was the proportion of patients experiencing any AEs (see Table 3). However, the frequency of ADRs showed the opposite trend, as the proportion of ADRs declined with increased risk category (see Table 5). These observations are likely related to the inherent increased risk and seriousness of events associated with the underlying diagnoses of

Table 5. Frequency of adverse drug reactions, serious adverse events, and serious adverse drug reactions by risk group

Risk group	Patients in group (n)	Patient-years	ADRs, n (%)	SAEs, n (%)	SADRs, n (%)
Low risk	25 790	81 332	383 (76.9)	187 (37.6)	72 (14.5)
Intermediate risk	10 369	43 385	311 (54.3)	351 (61.3)	89 (15.5)
High risk	1543	5759	80 (47.3)	118 (69.8)	29 (17.2)
Low-risk subgroups					
Non-SGA	20 448	61 693	307 (81.4)	122 (32.4)	52 (13.8)
SGA	5342	19 639	76 (62.8)	65 (53.7)	20 (16.5)

Abbreviations: ADR, adverse drug reaction; SADR, serious adverse drug reaction; SAE, serious adverse event; SGA, small for gestational age.
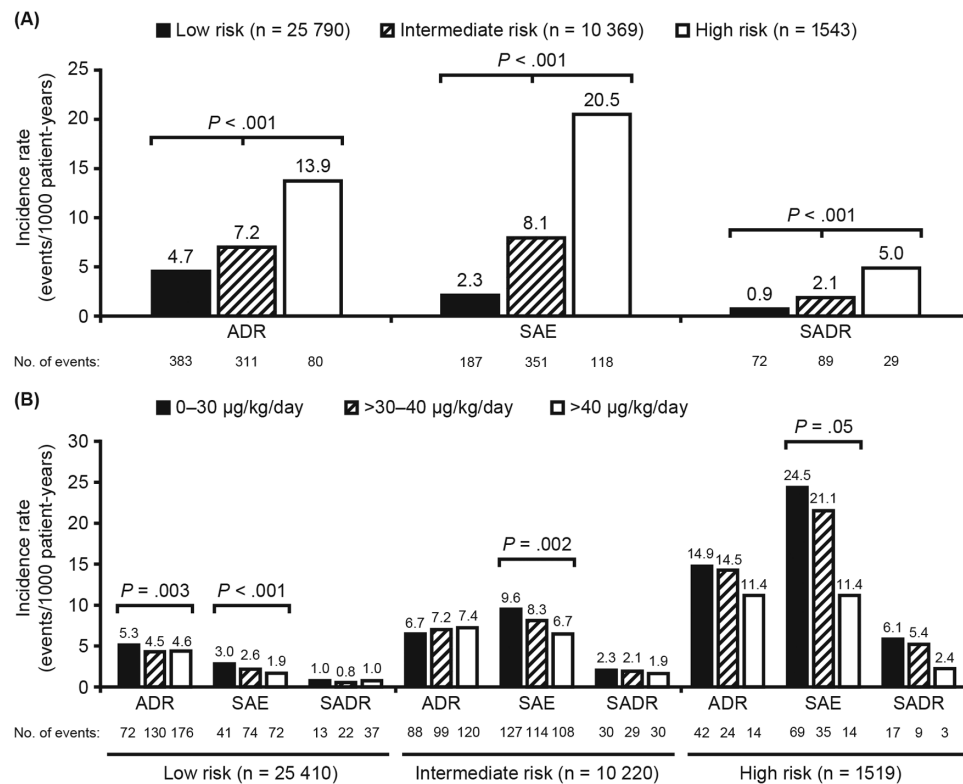
Figure 2. A, Incidence rates (events/1000 patient-years of exposure within the study period) for reported adverse drug reactions (ADRs), serious adverse events (SAEs), and serious adverse drug reactions (SADRs) by risk groups. B, Incidence rates for ADRs, SAEs, and SADRs by average growth hormone dose up to the first AE within each risk group. Only significant *P* values (< .05) are shown.

patients in the high-risk group (eg, chronic kidney disease and malignant tumors prior to GH treatment).

There was no evidence indicating an increased risk of experiencing AEs with increased GH dose. On the contrary, patients who experienced 1 or more AEs received a lower average GH dose up to the time of the AE onset, compared with the average dose for patients without any AEs. This result was consistent across risk groups and statistically significant in the low- and intermediate-risk groups and in the non-SGA low-risk subgroup (see Fig. 1). Similarly, we observed a significant decrease in incidence rates of ADRs and SAEs with the increasing average GH dose in the low-risk group (overall, and specifically in the non-SGA subgroup), and also in incidence rates of SAEs in the intermediate-and high-risk group. For the remaining groups and event types, the incidence of AEs appeared independent of the GH dose (see Fig. 2B).

The inverse relationship between AE incidence rates and GH dose may be partially explained by the practice of prescribing lower GH doses to patients who were overall more likely to experience AEs. This notion is supported by the decreasing mean GH dose at AE onset with the increasing risk category (38.4, 35.9, and 30.9 µg/kg/day in the low-, intermediate-, and high-risk groups, respectively). The relationship may also be partially driven by the

higher likelihood of experiencing some treatment-related AEs (eg, edema or increased ICP [8, 27]) in the early stage of GH treatment, while receiving a lower starting GH dose. Indeed, the proportion of patients experiencing ADRs was slightly elevated during the first year of GH treatment (see Fig. 4).

Within the low-risk group, incidence rates were significantly lower for ADRs, but significantly higher for SAEs in the SGA subgroup compared with the non-SGA subgroup. A similar pattern was observed in the previous analysis from NordiNet IOS (16). The frequency of SAEs among all AEs was 1.7-fold higher for SGA children compared with non-SGA children (see Table 5). However, the average GH dose prior to AE onset between these 2 groups was similar, despite a higher recommended dose for SGA (35 µg/kg/day in Europe and ≤ 67 µg/kg/day in the United States) compared with the GHD indication (25-35 µg/kg/day in Europe and 24-34 µg/kg/day in the United States). The higher incidence of SAEs in children born SGA may be related to their intrinsic higher morbidity profile compared with peers born appropriate for gestational age (28, 29).

The mean duration of GH treatment up to the onset of the first AE was quite long (2.3-2.9 years across risk groups). The duration of GH treatment up to the first AE, as well as the overall duration of GH treatment, was the
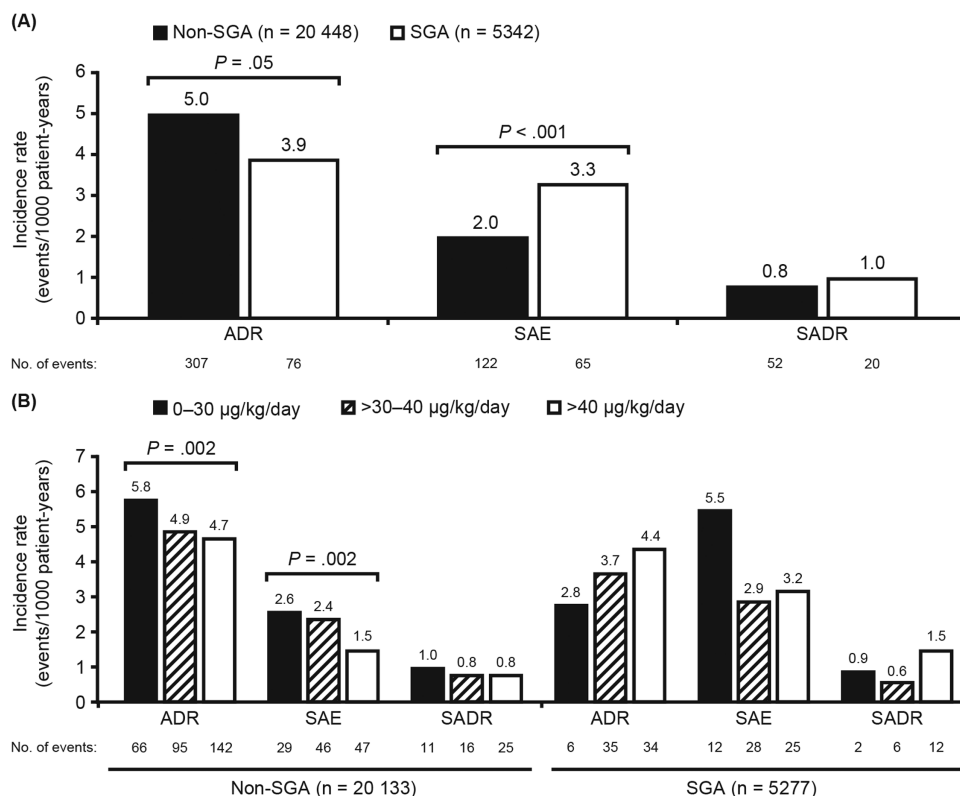
**Figure 3.** A, Incidence rates (events/1000 patient-years of exposure within the study period) for reported adverse drug reactions (ADRs), serious adverse events (SAEs), and serious adverse drug reactions (SADRs) in the low-risk group by subgroup (non–small for gestational age [SGA] vs SGA). B, Incidence rates for ADRs, SAEs, and SADRs by growth hormone dose up to the first AE in each subgroup. Only significant *P* values (< .05) are shown.
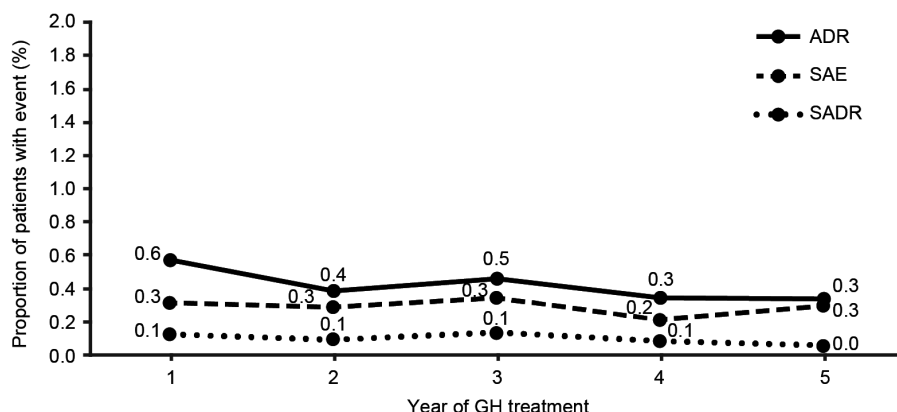
Figure 4. Proportion of patients with at least one adverse drug reaction (ADR), serious adverse event (SAE), or serious adverse drug reaction (SADR) of all patients exposed in a given year by duration of follow-up. GH, growth hormone.

longest in the intermediate-risk group. This could be partially explained by the relatively high proportion of patients with congenital conditions (eg, Turner syndrome), many of whom are diagnosed early in life. The proportion of patients experiencing AEs by year of follow-up remained quite stable throughout 5 years. This indicates that the

likelihood of experiencing AEs was low and relatively consistent throughout the duration of GH treatment.

Of the 62 neoplasms reported in this study, most (52%) were reported in the high-risk group. This was expected, as patients with an underlying history or risk for malignancy were included in the high-risk group, and the majority of
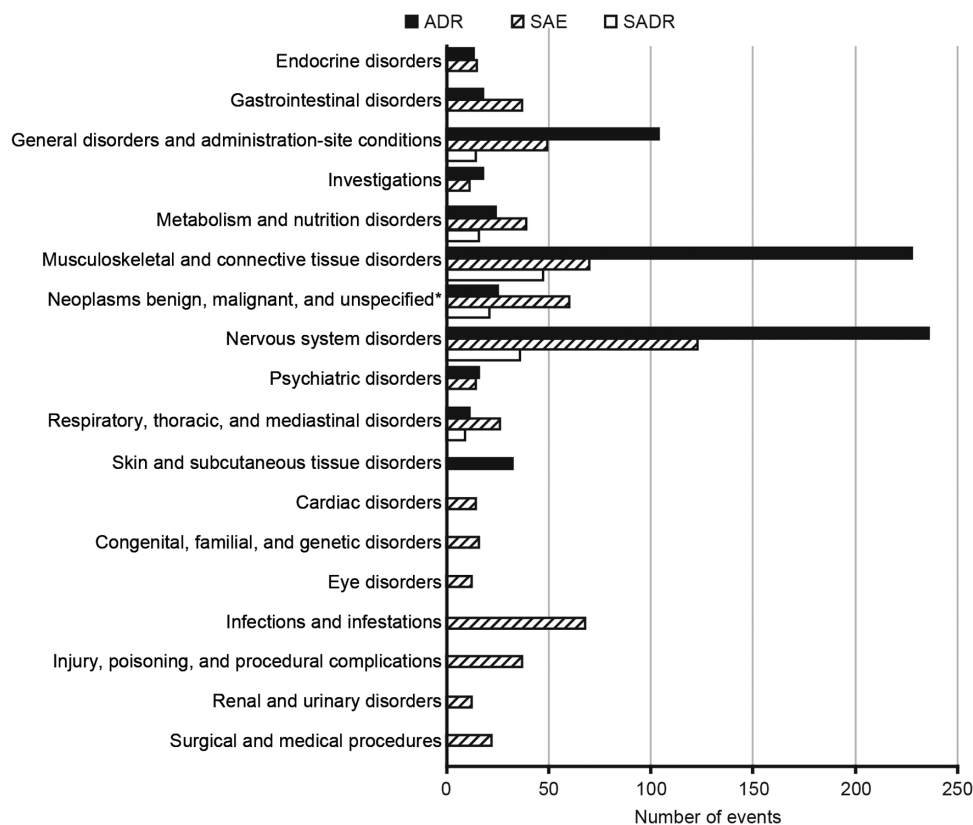
Figure 5. Frequency of adverse drug reactions (ADRs), serious adverse events (SAEs), and serious adverse drug reactions (SADRs) across all risk groups by system organ class (SOC). Only SOCs with more than 10 events are shown. *Including cysts and polyps.

the patients in this group (93%) had a previous medical history of a neoplasm before the start of GH treatment. There was a single case of osteosarcoma throughout the duration of the 2 studies, and it occurred in the high-risk group. This is in contrast with the French SAGhE study, in which 5 of 6874 low-risk patients experienced bone or cartilage tumors (13). Additionally, there were no cases of cerebral hemorrhage in the low-risk group in our study, which contrasts with the 7-fold increased mortality ratio due to cerebrovascular diseases in the French SAGhE cohort (12). However, as was later shown for the full SAGhE population, the elevated mortality risk in the low-risk patients was driven mainly by the French SGA subcohort (15). In addition, our data report events occurring during GH treatment, whereas SAGhE analyzed events occurring in older individuals who received GH treatment as children.

The lack of follow-up beyond the cutoff age of 20 years likely limits the potential of our data to capture the risk of developing noncommunicable diseases (eg, diabetes, cardiovascular morbidity, or neurodegenerative diseases) in older age. The etiology of such diseases can originate as early as during intrauterine development and early childhood, and is thus influenced by factors beyond genetic predisposition, for example, environmental factors (30, 31). In a recent

analysis of long-term risk of cardiovascular morbidity in Swedish patients treated with GH in childhood, the authors have partially accounted for this phenomenon (32). In addition to a long follow-up period of up to 25 years, each patient was matched with 15 control individuals from the general population matched for sex, birth year, and geographical region, and important covariates were included, such as birth characteristics and socioeconomic status (32). Capturing such a breadth of information is useful for retrospective analyses of long-term safety, as the baseline risk for noncommunicable diseases changes over time (33).

Among the 4 targeted AEs (SCFE, headache, increased ICP, and edema), only SCFE was the most common in the high-risk group. Notably, of the 21 cases of SCFE, 5 occurred in conditions with previously reported increased risk of SCFE (Turner syndrome, chronic renal insufficiency, and inflammatory bowel disease with presumed glucocorticoid treatment) (34-36). Patients experiencing SCFE also received a higher average GH dose up to the AE onset (43.7 μg/kg/day) compared with the whole patient population (30.9-38.6 μg/kg/day), which may have contributed to the rapid height velocity associated with SCFE (34), or to acute joint changes. Edema and increased ICP are likely related to the water retention and

temporary imbalance of cerebrospinal fluid production and resorption associated with GH treatment (20, 37), and thus possibly related to GH dose. Patients experiencing edema or ICP increase received a higher average GH dose (39.0-39.8 μg/kg/day) than the whole patient population, although this difference was less pronounced than in the patients with SCFE. It is possible that patients experiencing these targeted events had a relatively high sensitivity to GH. Given the possible link between the targeted events and GH dose, a gradual GH dose increase could be considered for future studies. Lastly, the patients who reported headache received similar average GH dose as patients in the low-risk group, which is where it was most frequently reported. Formulating hypotheses about the relationship between GH treatment and headache is limited by the low specificity of the symptom and the heterogeneity of concomitant diagnoses (Table S2 in the Supplementary Material [23]).

The strengths of our study lie in the pooling of data from 2 large observational studies with a similar design, which provide a greater number of cases for investigation of patient subgroups and infrequent events, as well as strengthening the statistical power of the data. The confidence in our findings is further underpinned by the methodical validation of data entry (18), systematic checking for outliers, and elimination of obvious data entry errors. The NordiNet IOS and the ANSWER Program were not constrained by a highly specific protocol, and offer an inclusive picture of the use and effectiveness of GH treatment in clinical practice.

Limitations of our study include the lack of an untreated control group, which limits the impact of drawing conclusions from the results. However, this is an inherent limitation of all noninterventional observational studies, and conducting a long-term randomized trial would be unfeasible and unethical. Given the multinational nature of our study, there is a potential for confounding of the results by local differences in diagnostics, laboratory analyses, and reporting of events among different clinics and countries, resulting in a potential lack of firm diagnoses in some patients. However, an earlier analysis of between-country reporting rates for AEs in the NordiNet IOS revealed no obvious differences (16). Limitations in the study design include data on AE-related discontinuations not systematically collected in either registry, and voluntary ascertainment that could introduce a bias and/or lead to incomplete data capture. Lastly, the patient cohort in the ANSWER Program had a large number of children with idiopathic short stature and isolated GHD. Because these groups have previously been shown to have fewer side effects (15), and the ANSWER Program cohort received higher GH doses in general (17), the relationship of higher doses to an increased incidence

of AEs could be diluted. However, we have addressed this potential concern by categorizing the patients into relevant risk groups and subgroups.

In summary, we found no indication of increased risk of mortality or incidence of AEs related to GH dose in any risk group. Our findings support a favorable benefit-risk profile of GH treatment across the indications included in the NordiNet IOS and the ANSWER Program.

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Additional Information

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