

Long-Term Safety of Recombinant Human Growth Hormone in Children

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Background: Between 1985 and 2006, the National Cooperative Growth Study (NCGS) monitored the safety and efficacy of recombinant human growth hormone (rhGH) in 54,996 children.

Methods: Enrolled patients were followed until rhGH discontinuation. Investigators submitted adverse event reports for targeted events or those potentially rhGH-related.

Results: Early concerns about *de novo* leukemia in patients without risk factors have not been substantiated—three observed vs. 5.6 expected in age-matched general population based on years at risk [standard incidence ratio (SIR), 0.54; 95% confidence interval (CI), 0.11–1.58]. *De novo* malignancies (intracranial and extracranial) were not significantly increased in patients without risk factors (29 confirmed vs. 26 expected; SIR, 1.12; 95% CI, 0.75–1.61). Second neoplasms occurred in 49 patients, of whom 37 had irradiation for their initial tumors (including five of 16 retinoblastoma patients, three of whom had bilateral retinoblastoma) consistent with an increased risk with rhGH. Thirty-three patients developed type 1 diabetes mellitus (DM) (37 expected; SIR, 0.90; 95% CI, 0.62–1.26). Type 2 DM and nonspecified DM were reported in 20 and eight patients, respectively. Two deaths were reported in patients with Prader-Willi syndrome and five deaths from aortic dissection in patients with Turner syndrome. In patients with organic GH deficiency and idiopathic panhypopituitarism, 11 events of acute adrenal insufficiency occurred, including four deaths, consistent with a reported increased risk for adrenal insufficiency in hypopituitary patients with or without rhGH treatment.

Conclusion: After more than 20 yr, leukemia, a major safety issue initially believed associated with GH, has not been confirmed, but other signals, including risk of second malignancies in patients previously treated with irradiation, have been detected or confirmed through the NCGS. These data further clarify the events associated with rhGH and, although confirming a favorable overall safety profile, they also highlight specific populations at potential risk. (*J Clin Endocrinol Metab* 95: 167–177, 2010)

In the more than 20 yr since recombinant human GH (rhGH) received Food and Drug Administration (FDA) approval for use in children in the United States, several hundred thousand children have received rhGH for the treatment of growth impairment. As previously reported, after approval of rhGH in 1985, Genentech, Inc., estab-

lished an open-label, multicenter, postmarketing surveillance study, the National Cooperative Growth Study (NCGS), to monitor the safety and efficacy of its rhGH products in children with growth disorders (1–8). Careful monitoring in the postmarketing setting is essential to adequately characterize the safety profile of a drug because

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For editorial see page 52

Abbreviations: AE, Adverse event; AI, adrenal insufficiency; CI, confidence interval; CNS, central nervous system; CRI, chronic renal insufficiency; DM, diabetes mellitus; GHD, GH deficiency; IH, intracranial hypertension; ISS, idiopathic short stature; OGH, organic GHD; PTLD, posttransplant lymphoproliferative disorder; PWS, Prader-Willi syndrome; rhGH, recombinant human GH; SAE, serious AE; SCFE, slipped capital femoral epiphysis; SIR, standard incidence ratio; TS, Turner syndrome.

rare adverse events (AEs) may not be detected in clinical trials in which a relatively small number of patients are exposed to the drug. Because spontaneous postmarketing reporting of AEs may be unreliable and incomplete and lack a denominator against which to calculate risk rates, registries such as the NCGS have been established to provide a more comprehensive and structured collection of safety data.

The cumulative enrollment in the NCGS from December 1985 to January 1, 2006, was 54,996 patients (65% males, 35% females), comprising 195,419 patient-years of treatment with Genentech's rhGH products. More than 900 investigators in North America participated. In this review, we present cumulative safety data for almost 55,000 patients up to January 1, 2006, and highlight areas of newly developed concern as well as those that no longer appear to be of concern.

Patients and Methods

Patients can enter the NCGS registry when a Genentech rhGH is initiated and can be followed until treatment is discontinued. Diagnostic demographics include idiopathic GH deficiency (42.5% of total enrollment), organic GH deficiency (OGHD; 15.2%), Turner syndrome (TS; 9.3%), chronic renal insufficiency (CRI; 3.2%), idiopathic short stature (ISS; 17.8%), and other conditions associated with growth failure ("Other"; 11.9%).

Details of NCGS patient monitoring have been reported (5, 6). Because NCGS is an open-label postmarketing registry with treatment as prescribed by the individual physician, there is no outside data-monitoring committee. Events are reviewed by the Genentech Drug Safety scientist. Safety data presented below are based on AE reports received by the Genentech Drug Safety Department (GDS) as of January 1, 2006, from NCGS sites. Investigators are instructed to submit an AE report for any event that may be potentially related to rhGH and to report all instances of targeted events [new or recurrent malignancies and central nervous system (CNS) tumors, and five events that have emerged in the past 20 yr as appearing to occur more frequently or be exacerbated in rhGH recipients: diabetes mellitus (DM), intracranial hypertension (IH), slipped capital femoral epiphysis (SCFE), scoliosis, and pancreatitis], whether or not they are considered rhGH related. Diagnostic parameters for these events are determined by the investigator. AEs that are reported to Genentech from patients who have discontinued GH or are taking GH but are not in the NCGS are also recorded in the Genentech safety database. Serious AEs (SAEs) are defined as events that are fatal, are life-threatening, require hospitalization, result in disability, are associated with a congenital anomaly or birth defect, or require medical or surgical intervention to prevent one of the described outcomes.

The frequencies of selected malignancies and DM were compared with age-adjusted background rates in the general pediatric population because there are few data for the ideal comparator population, untreated children with GH deficiency (GHD) or with other short stature diagnoses who might have

inherently increased risks regardless of rhGH use. For the malignancy analysis, only patients with new-onset tumors who did not have underlying factors that would have increased their risk (e.g. a prior malignancy, radiation exposure, bone marrow transplant, chemotherapy, neurofibromatosis, immunosuppressant use, and certain chromosomal disorders such as Down syndrome) were compared with the general population. For DM, comparison was performed only for those with type 1 disease because background rates for type 2 DM in pediatric patients are less readily available. Standard incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated for new-onset malignancies overall, for new-onset leukemia in patients without risk factors, and for new cases of type 1 DM. SIR represents the number of observed cases divided by the number of expected cases based on background rates in the age-adjusted general population applied to the years of rhGH exposure in each age group. Years of rhGH exposure were used rather than years at risk (time from initiation of rhGH therapy to the data cutoff point of January 1, 2006) because accurate reporting of events could be relied upon only during the period of rhGH exposure. Reported events occurring after rhGH was discontinued are not counted in the SIR analyses because we lack exact exposure and a denominator, but they are still included in the AE/SAE totals.

In the few instances where AEs are reported on NCGS forms but cannot be linked to an NCGS file in the clinical database due to anonymous identifier discrepancies, the AEs are also included in the results to err on the side of overidentification rather than underidentification of AEs/SAEs but are also not used in the SIR calculations. Categorization into diagnostic groups by etiology is determined from entry or follow-up information, which is not always complete or consistent over time. Thus, the number of patients in each diagnostic group can shift slightly as each new data assessment is programmed and data are culled. For this reason, we will occasionally use the term "approximately" in recognition of the potential for minimal differences.

Results

Overall safety findings

A total of 4084 AE reports were submitted to GDS from the NCGS as of January 1, 2006. Of these, 1559 were SAEs, including 174 deaths. Investigators assessed most of the reported deaths as being unrelated to rhGH or did not provide a causality assessment. The most common cause of death was CNS tumor (recurrence or new onset), primarily in patients with OGHD. Other causes of death included respiratory failure, pneumonia/pneumonitis, cardiac arrest, cerebral edema, accidental trauma, suicide, complications of renal failure, and sepsis.

Of the 174 deaths, 19 (11%) were assessed as related to rhGH by the investigator, four were designated as not assessable, and no causality was provided for 21. The majority of the 19 deaths assessed as related to rhGH (12 of 19) were due to neoplasms: craniopharyngioma (two), glioblastoma (two), medulloblastoma recurrence (two), astrocytoma (one), brain neoplasm (one), neuroblastoma

TABLE 1. Incidence of targeted events by indication

	All NCGS	IGHD	OGHD	TS	CRI	ISS	Other
n	54,996	23,393	8,351	5,127	1,778	9,778	6,569
AE	6.2	4.4	12.0	7.6	10.9	3.6	7.3
SAE	2.4	1.2	6.8	1.9	6.5	0.7	3.1
Deaths	0.3	0.1	1.0	0.1	1.2	0.0	0.5
Malignancy ^a	0.1	0.0	0.1	0.1	0.0	0.0	0.0
IC tumor recurrence	0.3	0.0	1.8	0.0	0.1	0.0	0.0
Leukemia ^{a,b}	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Second neoplasm	0.1	0.0	0.5	0.0	0.1	0.0	0.0
AI ^b	0.0	0.0	0.1	0.0	0.0	0.0	0.0
DM	0.1	0.0	0.1	0.2	0.2	0.1	0.2
IH	0.1	0.1	0.2	0.2	0.3	0.0	0.1
SCFE	0.1	0.1	0.4	0.2	0.3	0.0	0.1
Scoliosis	0.4	0.2	0.5	0.7	0.1	0.2	0.6
Pancreatitis	0.0	0.0	0.0	0.1	0.0	0.0	0.0

Data are expressed as percentage. IGHD, Idiopathic GHD; IC, intracranial.

^a New onset, no risk factors.

^b Based on fewer than 15 reports.

(one), optic tract glioma (one), osteosarcoma recurrence (one), and pineoblastoma (one).

The remaining deaths (7 of 19) were primarily isolated cases as follows: cerebral edema in a patient with a glioma resection, and cerebral edema in a patient with a mitochondrial myopathy and hypertrophic cardiomyopathy; arrhythmia in a patient with two renal transplants with hypertrophic cardiomyopathy and coronary atherosclerosis at autopsy; diabetic hyperosmolar coma in a patient with craniopharyngioma who was receiving rhGH at the time the hyperosmolar coma developed; depression after stopping rhGH in a 21-yr-old male with thalassemia major, with subsequent death from an overdose of “street drugs”; complications of neurofibromatosis in a patient with an optic glioma, an odontoma, ataxia, and facial swelling; and sudden death in a 4-yr-old male with Prader-Willi syndrome (PWS). A total of 130 deaths (75%) were assessed as unrelated to rhGH by the investigators.

In addition, we have previously reported that among 5127 TS patients, there were five deaths from aortic dissection/rupture (9). One occurred during a dilation procedure for coarctation, one was in a patient with a previous coarctation repair who had stopped rhGH 3 months before the death, and one was in a patient with bicuspid aortic valve. No previous cardiac history was provided for the remaining two patients, one of which was off rhGH for 21 months. No deaths related to this cardiovascular event were reported in any other patient group in NCGS.

Of the 511 NCGS-enrolled patients with PWS (1686 patient-years of rhGH exposure), two deaths were recorded and previously reported (10, 11). One, a 4-year-old obese male, died suddenly while asleep 67 d after first administration of rhGH. Snoring had worsened on treat-

ment, and bronchopneumonia was noted at autopsy (10). The other was a 7-yr-old male with preexisting cardiomegaly and other unspecified medical problems who died due to pulmonary hypertension and a presumed cardiac event after receiving rhGH for 6 months (11).

Among the 1778 patients with chronic renal failure, 22 deaths were reported, only one of which was assessed by the investigator as possibly related to rhGH. This patient had a history of two failed renal transplants and experienced a cardiac arrest approximately 3 d after his last hemodialysis session; hypertrophic cardiomyopathy was observed on autopsy. The remaining 21 deaths were described as unrelated to rhGH, or a causality assessment was not provided.

The frequencies of AEs, SAEs, deaths, and targeted AE categories by rhGH indication are presented in Table 1. Selected patient demographics and duration of rhGH therapy associated with these endpoints are listed in Table 2.

Targeted AEs associated with or exacerbated by rhGH

DM

DM has been reported in 65 patients; 37 (33 whose enrollment in NCGS could be confirmed) were classified as type 1, and 20 as type 2 (two in PWS); and eight were unclassifiable. The 33 type 1 DM cases, compared with that expected and adapted to an age-matched population (0–19 yr) (12), yielded a SIR of 0.90 and 95% CI of 0.62–1.26 (observed 33; expected 36.8).

Despite data documenting type 2 DM in the pediatric population (12), the increasing incidence (13), variance in frequency among ethnic groups, and diagnostic difficulties preclude us from assigning a SIR for this AE. However,

TABLE 2. Targeted events by demographics and treatment years

	Male (%)	Female (%)	Mean age at event (yr) ^c	Mean duration of GH treatment (yr)
All NCGS	65.0	35.0	10.3	3.6
All AE	60.0	40.0	12.0	4.6
SAE	61.0	39.0	11.9	4.4
Deaths	65.0	35.0	11.6	2.5
Malignancy ^a	54.0	46.0	12.4	3.8
IC tumor	59.0	41.0	11.6	4.3
recurrence				
Leukemia ^{a,b}	50.0	50.0	9.2	3.6
Second	56.0	44.0	13.8	3.1
neoplasm				
AI ^b	60.0	40.0	9.0	4.1
DM	57.0	43.0	14.0	4.4
IH	54.0	46.0	10.9	3.8
SCFE	64.0	36.0	13.8	3.9
Scoliosis	44.0	56.0	13.5	4.5
Pancreatitis ^b	43.0	57.0	13.4	3.2

IC, Intracranial.

^a New onset, no risk factors.

^b Based on fewer than 15 patients.

^c If the AE onset date is missing, the date of the AE report was used; for All NCGS, 10.3 yr is the mean age of enrollment.

to avoid underestimating the incidence of type 2 DM in NCGS compared with that expected in the general population, the eight unclassified cases are assumed to be type 2, totaling 28 cases, or an incidence rate of approximately 14 per 100,000 GH treatment-years.

IH

IH was reported in 61 confirmed NCGS patients. Approximately 60% of the events occurred within 6 months of starting GH, although 22% occurred after 2 yr. IH occurred at a higher rate in CRI, TS, and OGHD and at the lowest rate (two cases) in ISS (Table 1). Fourteen cases of unexplained papilledema were reported, but information was too limited to confirm as IH. Other NCGS patients developed elevated intracranial pressure due to underlying physical conditions (such as a CNS neoplasm or mitochondrial myopathy with cerebral edema and fatal outcome) that do not fall into the category of benign IH. Most IH resolved with discontinuation of GH or dose reduction. In five patients, there was an ongoing or irreversible adverse outcome (shunt procedure reported in three; “spotty” visual loss reported in one; persistent headaches and “visual problems” reported in one).

SCFE

SCFE was reported in 93 patients. Of these, 68 were unilateral (or unspecified), and 25 had bilateral involve-

ment. Most patients underwent surgical pinning of the hip(s). Rapid growth, obesity, trauma, and radiation exposure were among the risk factors reported. Patients with TS, OGHD, and CRI have the greatest proportionate risk compared with other etiologies (Table 1). Thirty-one other patients had a SCFE event before entering the NCGS; none of these patients had a SCFE event while being followed in the NCGS.

Scoliosis

Overall, scoliosis was reported in 238 patients; 76 were described as progression of preexisting scoliosis. Scoliosis was classified as new onset or a prior history was not specified in 162. Scoliosis was more common in TS compared with the other etiologies in Table 1. However, in the “Others” group, there were three reports in 511 PWS patients, which is the same as the TS rate (0.6%). Most events (73%) were described as nonserious. Among the 64 patients with serious scoliosis, 37 reported surgical treatment.

Pancreatitis

Ten patients developed pancreatitis during rhGH treatment, and one case was reported approximately 5 months after rhGH discontinuation. Nine were hospitalized. The growth disorders in these patients include three cases of TS (one with preexisting DM and ketoacidosis during the episode), two cases of GHD, and the rest with assorted syndromes. Of these, four had possible risk factors for the development of pancreatitis (including use of corticosteroids or valproic acid or pseudohypoparathyroidism). ISS was the diagnosis only in the case that developed 5 months after rhGH was stopped. Given an estimated background rate of 3.6 per 100,000 patient years in the pediatric age group (14) and an exposure of 192,345 patient-years of rhGH treatment, the 10 GH-treated cases yield an SIR of 1.44 and 95% CI of 0.70–2.67.

Adrenal insufficiency (AI): a new targeted association

In patients with OGHD and idiopathic panhypopituitarism, 11 events consistent with acute AI, including four deaths, were recorded. The time from onset of rhGH therapy to the event of AI ranged from within 24 h of initiation to 7.4 yr, with a mean of 2.5 yr. Five nonfatal cases were assessed as serious by the investigator. The remaining two cases were assessed as nonserious. The four fatal cases of AI were: 1) a 4-yr-old female with GHD secondary to septo-optic dysplasia and a history of episodes of adrenal crisis precipitated by viral infections who died from a respiratory syncytial virus infection with associated acute adrenal crisis despite reported “stress doses” of corticosteroids; 2) a 12-yr-old female with GHD secondary to

TABLE 3. New-onset malignancies in patients without risk factors: tumor types in two or more patients

Malignancy	No. of patients (%)
Unspecified brain neoplasm	5 (13.8)
Glioma	4 (11.1)
Lymphoma	4 (11.1)
Leukemia	3 (8.3)
Thyroid carcinoma	3 (8.3)
Astrocytoma	2 (5.5)
Germ cell tumor	2 (5.5)
Osteogenic sarcoma	2 (5.5)
Soft tissue sarcoma	2 (5.5)
Other	9 (25.0)
Total	36 (100)

craniopharyngioma on long-term steroid replacement. One day after her first dose of rhGH, she developed fever, vomiting, diarrhea, and hypotension, and while in an emergency room experienced a cardiac arrest. She was treated with iv steroids, but expired 3 d later; 3) an 11-yr-old male with panhypopituitarism due to a hematological malignancy with CNS involvement, who was receiving steroid replacement. Five weeks after rhGH was started, the patient expired at home. Splenomegaly and an atrophic pituitary were noted on autopsy; and 4) a 3-yr-old male with idiopathic panhypopituitarism who died at home 5 months after starting rhGH. He “felt ill” on the day of death but was not evaluated by a physician. A culture was reported as positive for influenza A.

Malignancies

Malignancies overall

Intracranial malignancies of nonpituitary origin were reported in 243 patients; 199 were recurring tumors, and 44 were new-onset malignancies. Of the 44 new-onset intracranial malignancies, 29 had previously defined factors that would increase the risk of developing a new malignancy (including a history of a different primary malignancy as described in *Second neoplasms* below), and 15 were unassociated with these factors.

Extracranial malignancies, including leukemia, were reported in 87 patients; 24 were recurring, and 63 were

new-onset malignancies. These figures exclude premalignant lesions or recurrent/new-onset histiocytosis X. Of the 63 new-onset tumors, 42 were associated with previously defined factors that would increase the risk of developing a new malignancy, and 21 were not.

The malignancy types for the 36 cases of new-onset intracranial or extracranial malignancies without prior risk factors are listed in Table 3. Among these, enrollment status in NCGS was confirmed in 29, and the remaining seven may have been spontaneous reports. In Table 4, we compared only the 29 patients confirmed as being enrolled in NCGS to the general population by age group for an SIR analysis because we knew their exposure to rhGH. Overall, the SIR (see *Patients and Methods*) was 1.12 and 95% CI was 0.75–1.61.

Leukemia

Twenty-seven cases of leukemia, including nine recurrences, 15 new events, and three cases after rhGH discontinuation, were reported. Of the 15 new cases, 12 had risk factors and three did not. The latter three were of two types: acute lymphocytic leukemia ($n = 2$) and erythroid leukemia ($n = 1$). The SIR for new-onset leukemia without associated risk factors compared with that in the age-matched general population is 0.54; 95% CI, 0.11–1.58 (observed number of cases, three; expected number of cases, 5.6). The three cases identified after rhGH discontinuation did not have risk factors, but these are not included in the SIR analysis because years of exposure (time on therapy) rather than years at risk are used for this analysis.

Second neoplasms

There were approximately 1500 patients with a history of an intracranial malignancy at baseline after excluding those with craniopharyngiomas. In addition, there were 1000 patients with a history of a variety of extracranial malignancies at baseline, and the total number of intracranial and extracranial NCGS malignancies at baseline was 2500. Among these 2500 patients with a history of malignancy, 49 (2%) second neoplasms developed after enrollment. Thirty-seven of these 49 patients were re-

TABLE 4. New-onset malignancies without risk factors

Age (yr)	Years of GH exposure	Expected rate per 100,000 yr of exposure	Observed cases	Expected cases
0–4	11,348	20.4	1	2.32
5–9	44,585	11.4	6	5.08
10–14	85,909	12.9	12	11.08
15–19	36,082	20.0	9	7.22
20–24	540	34.9	1	0.19
Total	178,464	14.5 ^a	29	25.88

SIR, 1.12; 95% CI, 0.75, 1.61.

^a Age-standardized expected rate.

ported to have received radiation for their initial tumor. The most common second neoplasms were glioblastoma/glioma (n = 14), osteogenic sarcoma (n = 7), astrocytoma (n = 7), leukemia (n = 5), meningioma (n = 3), and mucoepidermoid carcinoma (n = 3).

Leukemia was the primary malignancy most commonly associated with the development of a second neoplasm. Among the 49 patients developing second neoplasms, 18 had a history of leukemia (all types combined, including one report of myelodysplastic syndrome) as their primary malignancy. Retinoblastoma was the primary malignancy in 16 patients, of whom five developed second neoplasms [one osteogenic sarcoma, one rhabdomyosarcoma followed by osteogenic sarcoma, one malignant fibrous histiocytoma (developed 5 months after rhGH started), one glioblastoma, and one meningioma]. Four of the five secondary malignancies occurred in patients who had undergone prior radiation, and three occurred in patients with bilateral retinoblastomas (osteogenic sarcoma, rhabdomyosarcoma followed by osteogenic sarcoma, and meningioma).

For the 49 secondary malignancies, the calculated rhGH exposure time was 4.3 yr; the total patient-years, 10,750; and the number of cases per 1000 patient-years, approximately 4.6.

Among the 994 patients with craniopharyngioma, only three secondary neoplasms developed; these included (one each) acute lymphocytic leukemia, astrocytoma, and brain stem glioma.

Posttransplant lymphoproliferative disorder (PTLD)

Among approximately 300 patients who had undergone a renal transplant and were followed in NCGS, three developed PTLD. One renal transplant patient was a 16-yr-old male who developed a high-grade abdominal lymphoma 1½ yr after rhGH; the lymphoma was treated but recurred, leading to bowel perforation and death. A second was a 16-yr-old male diagnosed with PTLD approximately 1 yr after starting rhGH. rhGH therapy was discontinued, but no follow-up information was reported. The third case was a 12-yr-old male, diagnosed with a lymphoma approximately 4 months after starting rhGH therapy and approximately 10 yr after renal transplant. rhGH was discontinued, but no follow-up information was reported. In addition, PTLD was reported in one 10-yr-old female, 5 months after rhGH, among 17 NCGS-enrolled patients with prior liver transplantation. All four patients with PTLD received concomitant immunosuppressive therapy. There were no other malignancies reported among NCGS renal transplant patients, including no reports of renal cell carcinoma. Furthermore, there were no reports of renal cell carcinoma among all NCGS patients.

Tumor recurrence: intracranial

At baseline, just over 2500 patients enrolled in the NCGS had a history of a nonpituitary CNS tumor. Recurrences were reported in 199 patients (approximately 7.9% of those with baseline tumors). The largest single category of intracranial tumor was craniopharyngioma, with 994 patients at baseline and 86 reports of recurrence (approximately 8.7%).

Discussion

This report updates the NCGS experience with nearly 55,000 children who have received Genentech's rhGH products through January 1, 2006. This degree of postmarketing surveillance was initially prompted, in part, by the catastrophic finding of deaths resulting from Creutzfeldt-Jakob infection in recipients of human pituitary GH (15) and sustained by reports of an increase in leukemia in children receiving both human and recombinant GH (16). Although subsequent years of experience have failed to confirm an increased incidence of leukemia in patients without preexisting risk factors (17), including this current report as discussed below, new safety signals of events potentially associated with rhGH treatment, including the risk of secondary malignancies after irradiation (18), deaths from AI (19), and deaths in PWS (10, 11, 20), have emerged. Thus, a comprehensive retrospective review of cumulative data is warranted.

Overall safety and deaths

The overall incidence of AEs and SAEs from the NCGS continues to be stable, compared with prior NCGS safety analyses (4). The GH indications with the highest incidence of overall AEs and SAEs are OGHD and CRI (Table 1), as expected based on the severity of the underlying medical conditions in these patients. The ISS indication has the lowest incidence of all events. Of the 174 deaths, the most common cause was CNS tumor (recurrence or new onset), and the GH indications with the highest numbers of deaths proportionally were OGHD and then CRI. When causality was reported, cause of death in the majority of patients was assessed by the investigator as unrelated to rhGH. Specific groups were identified as being at risk for sudden death (including TS, from aortic dissection and rupture; PWS, from respiratory failure; and ACTH-deficient patients, from AI).

Targeted AEs associated with or exacerbated by rhGH

The targeted events reported here include scoliosis, pancreatitis, SCFE, IH, DM, and AI. The overall incidences of each category remain infrequent ($\leq 1\%$), and the

first five are comparable to our last NCGS overall safety report in 2000 (4). For scoliosis, the majority of the reports are for new-onset or unspecified and are reported as non-serious. The highest in our diagnostic groups is that of TS, which is known to have an increased incidence of scoliosis in untreated patients (21), although in the “Other” group the incidence in PWS is equal to that of TS. Pancreatitis and its association with rhGH therapy were first reported in 1995, when 11 cases were known to the FDA (22). Currently, there are three NCGS reports in TS, seven in all other pathological diagnoses, and one in ISS after cessation of rhGH. A mechanism linking pancreatitis with rhGH or the underlying disorders has not been described, although recent data suggest that the incidence of pancreatitis overall is increasing in children (23, 24). Several NCGS patients had underlying pathology that could predispose to pancreatitis (pseudohypoparathyroidism, valproate therapy, corticosteroid use, and diabetes) independent of rhGH use. Nevertheless, unexplained abdominal pain in children being treated with rhGH, especially if they have predisposing risk factors or have TS, should be evaluated carefully.

The current frequency of SCFE in patients treated with rhGH therapy is comparable to that previously reported from the NCGS (25). SCFE is associated with obesity (26), untreated endocrine conditions that affect growth (*e.g.* hypothyroidism and GHD) (27), and growth during puberty (28). These factors as well as trauma and radiation exposure were among the risk factors associated with SCFE in the NCGS cohort as well. In TS, the underlying SHOX deficiency may also play a predisposing role. Although IH associated with GH therapy was previously documented by NCGS data (29), a mechanism has not been defined. However, its occurrence with rhGH treatment appears greater in groups at higher risk for other reasons. Patients with CRI were reported to have an increased risk of IH independent of rhGH therapy (7) and have the highest rate in the NCGS database. TS patients have the next highest rate, and two previous case reports suggest that they, too, may be predisposed (30, 31). ISS patients, with few to no risk factors, had only two events and have the lowest rate in NCGS. Although the ISS rate exceeds the annual incidence estimate of 0.9 per 100,000 children (32) in the general pediatric population, cross-study comparisons should be interpreted cautiously.

The incidence of type 1 DM was not increased by rhGH therapy. The incidence of type 2 DM (14 per 100,000) appears to be less than that reported from the Pharmacia KIGS database (34.4 per 100,000) in 2000 (33), which might reflect differences in ascertainment and reporting, as well as different study populations with variable risk factors for the development of DM. Our data exceed the

incidence of type 2 DM in an earlier report (34) [a 10-fold rise (from 0.7 to 7 per 100,000) in the general U.S. pediatric population], but it is more consistent with the data from the 15- to 19-yr-old minority groups described in the SEARCH epidemiological study of DM in U.S. youth aged below 20 yr (12). Although insulin resistance is associated with GH therapy, it is usually transient, compensated for by increased insulin levels, and reversible, and it rarely leads to overt diabetes. Thus, the increase in type 2 DM in the general pediatric population first reported in 1996 (34) and confirmed to be further increasing in 2007 (12, 13) may partly explain the incidence in NCGS.

There were 11 AE reports due to AI, with four fatalities, three of which appear to have been associated with the stress of infection. Although there are no published comparator rates from pediatric populations, the rate of AI in NCGS (200 per 1 million NCGS population) is within the range of published rates of secondary AI (150–280 per million population) in the general population (35). As reported by Mills *et al.* (19), there is a much higher than expected death rate in children with AI than in the general population. GH affects the metabolism of glucocorticoids through several pathways. Clinically, it has a modulating effect on hepatic 11 β -hydroxysteroid dehydrogenase 1, decreasing the conversion of cortisone to cortisol (36, 37). Thus, in GHD patients endogenous cortisol can decrease after GH treatment is initiated. Through the same mechanism, GH therapy in severe GHD may also unmask previously unsuspected central hypoadrenalism (38). In addition, whereas patients on cortisone replacement therapy are more vulnerable to the inhibitory effect of GH on 11 β -hydroxysteroid dehydrogenase 1 than those on hydrocortisone (39), caution must be exercised regardless of the type of steroid replacement. GH also enhances the activity of CYP3A4, a cytochrome P450 enzyme involved in glucocorticoid catabolism (40). Thus, rhGH therapy may both unmask unsuspected ACTH deficiency and negate low replacement glucocorticoid doses used in secondary AI by decreasing the availability of cortisol. Patients starting GH therapy may require adjustments in their glucocorticoid replacement doses, and stress doses if calculated as a multiple of low daily doses may be insufficient if not increased. Although rhGH may facilitate the occurrence of AI, patients with hypopituitarism are at lifelong risk for AI and sudden death and need proactive counseling and medical attention, whether or not they are receiving rhGH (19).

Events in specific categories with unusual safety issues

Maligancies

Because GH is a known mitogenic agent and IGF-I has antiapoptotic effects, there has been ongoing concern

about the oncogenic potential of rhGH therapy. Although the NCGS report, based on 33,000 patients in 2000, was reassuring (4), the current data now comprise 20 yr of GH therapy, 54,996 patients, and a cumulative 192,345 patient-years of treatment. With the longer time and expanded patient numbers, we continue to see no increase in new malignancies or recurrences of CNS tumors in rhGH-treated children without risk factors, consistent with other reports (18, 41). The low number of cases of new-onset leukemia without risk factors also confirms previous reports that GH therapy does not increase the incidence of leukemia in children not at risk (17, 18, 41). The three cases without risk factors reported after GH discontinuation, which were not counted, do not change this conclusion because at least 12 cases would have been needed in the 55,000-patient cohort to demonstrate a positive relationship to rhGH (statistically significant SIR greater than 1).

Second tumors were seen in 49 of the approximately 2500 patients enrolled in the NCGS who had a prior history of malignancy (excluding craniopharyngioma) or approximately 4.6 cases per 1000 patient-years of rhGH exposure. Overall, the dominant risk factor appears to be a prior exposure to radiation. CNS tumors, followed by osteogenic sarcoma, were the most frequently reported second neoplasms. The most common primary malignancy associated with the development of second neoplasms was leukemia. However, proportionately, patients with retinoblastoma had a higher frequency of second neoplasms; four malignancies and one meningioma developed in 16 patients with retinoblastoma. Three of these patients had bilateral retinoblastomas consistent with a germline mutation. In these there is an estimated 500–2000 times greater genetic risk of developing a new malignancy, particularly an osteosarcoma, independent of radiotherapy and clearly independent of rhGH (42).

That our data are consistent with an increase in the occurrence of second malignant tumors in children treated with rhGH is of some concern. Although the risk of developing a new tumor in any patient with a past malignancy is elevated regardless of rhGH therapy, this risk in those with a prior malignancy appears to be further increased by rhGH. Thus, these patients and their families should be counseled on risks, whether GH-related or not, before commencing therapy. The increased risk of developing second neoplasms in GH-treated childhood cancer survivors is now listed in U.S. labeling for all rhGH products.

A drawback of NCGS and similar GH registries is that there is no compulsory reporting system for new AE data after discontinuation, and new tumors may occur years after therapy has ended. Nevertheless, our conclusions are

consistent with those of the long-term retrospective study report by Sklar *et al.* (18) on a large cohort of childhood cancer survivors, the Childhood Cancer Survivor Study (CCSS), which tracked 5-yr survivors of cancers that occurred before age 21 and were diagnosed between 1970 and 1986. In Sklar's series of 13,222 patients, the adjusted relative risk of a second neoplasm for GH-treated survivors compared with those not treated with GH was 3.21 (95% CI, 1.88–5.46; $P < 0.0001$). They reported seven patients with second malignancies during GH therapy and eight after therapy discontinuation. Because second neoplasms from NCGS are counted in those receiving rhGH, the appropriate comparator numbers from Sklar data are 354 patients with an average GH exposure of 4.6 yr before the second neoplasm in seven patients. Therefore, the total GH exposure was approximately 4.6 yr \times 354 patients or 1628 patient-years. With seven second neoplasms, the number per 1000 patient-years is approximately 4.3 and is comparable to the incidence observed in NCGS (4.6 cases per 1000 patient-years). As in NCGS, radiation exposure was the major risk factor in the Sklar series; all but one of 14 evaluable second tumors developed in a site previously exposed to radiation. Although Sklar's data adjusted for radiation exposure, it does not appear that they adjusted for dose, so we cannot be sure that the exposure in our cohort was the same. In addition, a recent CCSS data update from the same cohort assessed some years later showed a decreased relative risk for second tumors in GH-treated patients (2.15; 95% CI, 1.33–3.47; $P < 0.002$) (43). The decrease was attributed in part to the incidence of second tumors in the non-GH-treated group increasing more rapidly than in the GH-treated group, raising the question of whether GH treatment is accelerating the appearance of tumors that might otherwise occur spontaneously with time.

The issue of the risk of PTLD in patients having received rhGH before renal transplantation was recently described in data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) (44). Among patients with CRI who later received a renal transplant, rates of PTLD after transplantation were higher in those who had used rhGH before transplantation (18 of 407 or 4.4%) compared with CRI patients who had never used rhGH (23 of 1240 or 1.9%; $P = 0.009$). However, pre-transplant rhGH users were split into CRI and dialysis groups, and rhGH use in the group on dialysis before transplantation was not associated with a higher rate of PTLD after transplantation. Thus, only the CRI subset analysis and not the full NAPRTCS dataset was significant. Furthermore, the Epstein-Barr virus status of the patients before receiving posttransplant immunosuppressive therapy was not reported, so no matching data for this risk

factor were reported. The rate of PTLD in patients who started rhGH posttransplant was actually lower than in the nonusers (1.25 vs. 2.18%; $P = 0.07$), although this should theoretically be the period of greatest risk. Furthermore, there were only three reports of PTLD out of approximately 300 renal transplant patients in the NCGS, which indicates an incidence rate in the 1% range, a figure consistent with background rates of PTLD in the general pediatric population after renal transplantation (1.2 to 4.5%) (45, 46). The PTLD issue raised the question of GH effects on development of other malignancies in renal transplant patients (47), particularly the risk of posttransplant renal carcinoma. This issue was raised when it developed in two GH-treated patients followed in the European KIGS registry (48). There have been no cases of renal cell carcinoma in the NCGS, either in renal patients or other patients.

PWS

Among the 511 NCGS patients with PWS, there have been two deaths (0.44%) (10, 11). With 1686 patient-years of rhGH exposure, the incidence is 0.1% per year. The background PWS mortality rate is elevated and in one cross-sectional epidemiological study was cited as approximately 3% per year (49). However, this rate is probably not applicable to NCGS findings because the mortality rate from that study was estimated across all ages, whereas only deaths occurring during rhGH treatment are captured in NCGS, and the mean age ± 1 SD of these patients is 7.9 ± 4.4 yr. Other applicable background rates are not available. In the reports and reviews of death in PWS children receiving rhGH therapy in the literature, the majority of patients were reported to have been severely obese and to have died from respiratory insufficiency; most of these had respiratory symptoms before rhGH therapy. Most of the deaths occurred during the first 9 months of rhGH therapy, and the two in the NCGS were within 6 months. The temporal relationship to the onset of rhGH therapy implies that an enhanced drug-related risk at the start of therapy cannot be excluded (11, 20, 50). In addition, two recent reports from a single study suggest that central AI may be present in PWS under stressful conditions and could be associated with central apnea and contribute to sudden death, without a link to rhGH treatment *per se* (51, 52). Nevertheless, severe obesity and respiratory impairment in PWS patients remain contraindications to GH therapy, as per the product label, and pretreatment evaluation for evidence of airway obstruction and sleep apnea is recommended. Currently, there are no guidelines for monitoring adrenal function in these patients.

Summary and conclusions

This report summarizes the safety of rhGH therapy over its first 20 yr based on the NCGS experience. The overall safety profile of rhGH continues to be favorable, but careful monitoring for the presence of certain conditions is important both during and after therapy. Children with prior malignancies show an increase in the incidence of second tumors, especially if treatment of the primary malignancy involved radiation therapy; children with bilateral retinoblastoma are at risk based on their underlying predisposition to develop second malignancies. Patients with an active malignancy should not receive rhGH, and patients with a history of a prior malignancy whose tumor is no longer active should be carefully monitored for any evidence of progression or recurrence. Children with OGDH may develop AI or experience adrenal crises. Baseline and stress doses of glucocorticoids may need to be evaluated and adjusted when GH therapy is initiated. Children with PWS have orthopedic and metabolic risks, are particularly vulnerable to airway obstruction and infections, and should be evaluated for respiratory compromise before starting GH therapy, then followed carefully thereafter. Children with TS are at risk for aortic dissection and rupture, which should be considered in the differential diagnosis of chest pain and pulmonary distress in these patients, although there is no evidence that rhGH increases their risk. Children with CRI have a higher risk of mortality compared with others treated with GH, although only one of the deaths in this study was attributed to rhGH. Because rhGH therapy may increase insulin resistance, patients using rhGH should be appropriately monitored. Patients with TS, CRI, and PWS may be at increased risk for IH, although all should be monitored. Although ISS patients are at the lowest risk for all associated complications and the AEs described in the at-risk groups still remain low, continued vigilance on the part of the practitioner remains the most effective way to ensure long-term safety.

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