LONG-TERM OUTCOMES

OF HGH TREATMENT IN CHILDHOOD

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Disclosure

The speaker wishes to disclose that he has received honorarium as speaker consultant from the following pharmaceutical companies: NovoNordisk, and Pfizer.

Also has stocks at Insulet Corp., Exact Sciences Corp., and Mannkind Corp.

Objectives

- Review study “Safety and Appropriateness of GH treatment in Europe (SAGhE)” findings
- Address risks associated to:
  - Excessive GH states
  - GH deficiency states
  - recombinant GH (rGH) use & its dosages
- Look into evidence-based: Authorities’ positions regarding efficacy, safety, and use rGH

Background

- 1985 rGH became available.
- Manufactured offered the possibility of unlimited supply.
- This buttressed the expansion of GH for use in pts with GH sufficiency and short stature: e.g., Turner syndrome, renal failure, Prader-Willi syndrome, SGA and idiopathic short stature.
- GH use expanded from physiologic hormone replacement to pharmacologic, growth enhancing use.

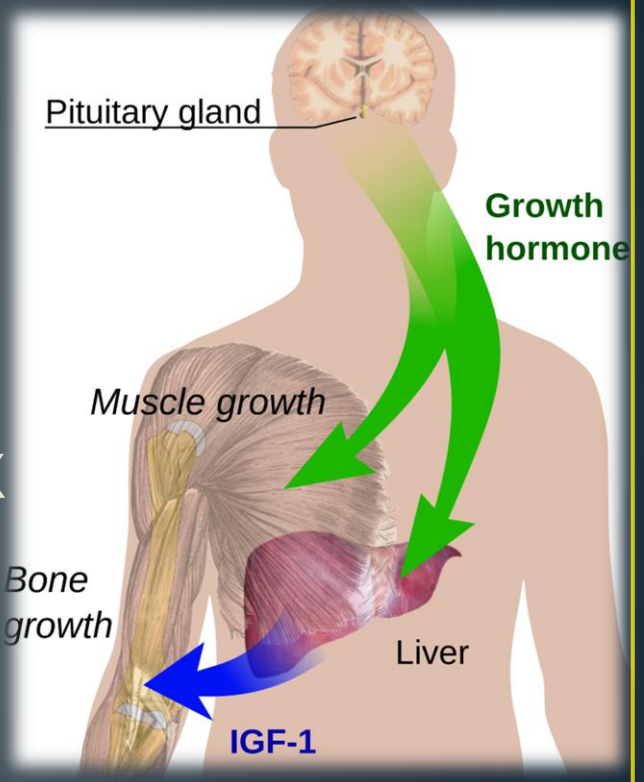
GH excess states - Acromegaly

- Pts w/ acromegaly secrete more GH than what is given to pts pharmacologically, but the morbidities experienced by these pts gave clues to potential short- and long-term adverse effects of GH treatment.
- Pts w/ acromegaly experience: IGTT and T2DM, edema, joint pains and arthritis, HBP, sleep apnea, and cardiomyopathy.

Endocr Pract. 2011;17(Suppl 4):1–44.

GH excess states - Acromegaly

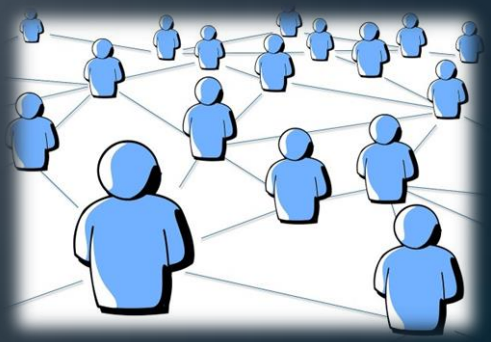
- They may also be at higher risk for cancer, particularly of the colon, w/ some reports stating that cancer mortality is higher.
- Acromegaly is also associated with a 2X increased mortality risk, with evidence suggesting that normalizing GH levels decreases mortality risk.



Katznelson L, Atkinson JL, Cook DM, et al. AACE medical guidelines for clinical practice for the diagnosis and treatment of acromegaly—2011 update. Endocr Pract. 2011;17(Suppl 4):1–44.

National Cooperative Growth Study (NCGS)

- Data > 20 years from the NCGS, ~ 55,000 pts treated with GH, ~ 200,000 pt-yrs of treatment.
- All indications for GH treatment were included in the analysis.
- 174 deaths were reported, of which 19 were reported to be related to GH treatment, 12 of which were neoplasms.



Bell J, Parker KL, Swinford RD, et al. Long-term safety of recombinant human growth hormone in children. *J Clin Endocrinol Metab*. 2010; 95:167–177.

NCGS

- The causes of the other 7 deaths varied from overdose to the sudden death associated with Prader-Willi syndrome.
- 29 cases of confirmed new onset malignancies in treated children, (expected 26 cases), given an incidence ratio of 1.12; but the numbers were too low to establish significance.
- Overall safety profile of rGH continues to be favorable, but careful monitoring for the presence of certain conditions is important both during and after therapy.

Bell J, Parker KL, Swinford RD, et al. Long-term safety of recombinant human growth hormone in children. *J Clin Endocrinol Metab*. 2010; 95:167–177.

NCGS

- Incidence of 2nd tumors, especially if treatment of the 1ry malignancy involved radiation therapy.
- Pts w/ an active malignancy should not receive rGH, and pts w/ a history of a prior malignancy whose tumor is no longer active should be carefully monitored for any evidence of progression or recurrence.

Bell J, Parker KL, Swinford RD, et al. Long-term safety of recombinant human growth hormone in children. *J Clin Endocrinol Metab*. 2010; 95:167–177.

NCGS

- Children with GHD may develop adrenal insufficiency.
- **No** deaths related to cardiovascular events were reported in any other patient group in NCGS but 5 TS out of 5127 treated --i.e., aortic dissection.

Bell J, Parker KL, Swinford RD, et al. Long-term safety of recombinant human growth hormone in children. *J Clin Endocrinol Metab*. 2010; 95:167–177.

S'informer

> Actualité

Points d'information

Informations de sécurité

Communiqués

> **Communiqués / Points presse**

Travaux de l'Agence Européenne des Médicaments (EMA)

> **Répertoire des médicaments**

> **Autorisation et déclaration**

← précédent

Hormone de Croissance synthétique (somatropine recombinante) : Premiers résultats de l'étude épidémiologique sur la tolérance à long terme - Communiqué

10/12/2010

Med

Lire aussi

- Hormone de Croissance recombinante (somatropine recombinante) : actualisation des données sur le rapport bénéfice/risque - Lettre aux professionnels de santé (08/08/2011)
- Hormone de Croissance recombinante (somatropine recombinante) : Premiers résultats de l'étude épidémiologique sur la tolérance à long terme - Lettre aux professionnels de santé (10/12/2010) (78 ko) (10/12/2010)
- Hormone de Croissance recombinante (somatropine recombinante) : Premiers résultats de l'étude épidémiologique sur la tolérance à long terme (SAGhE)- Questions/réponses (10/12/2010) (78 ko)

Le numéro vert est fermé

Les premiers résultats indiquent un risque de surmortalité toutes causes confondues par rapport à la population générale (93 décès constatés dans cette cohorte contre 70 estimés dans une population de référence en France). Ce risque est en particulier augmenté chez les patients ayant reçu de fortes doses, au-delà de celles recommandées dans les AMM actuelles. Les données ne montrent pas d'augmentation de la mortalité globale par cancer (tous cancers confondus). Elles suggèrent une surmortalité liée à la survenue de complications vasculaires cérébrales (telles que des hémorragies intra-cérébrales) et de tumeurs osseuses.

"Early results indicate a risk of mortality from all causes compared with the general population (93 deaths observed in this cohort against 70 estimated in a reference population in France)."

European Medicines Agency to review the safety of somatropin-containing medicines

Press release

10/12/2010

European Medicines Agency to review the safety of somatropin-containing medicines

The European Medicines Agency is starting a review of the safety of somatropin-containing medicines authorised centrally or by national procedures in the European Union (EU). The review will look into all available data on somatropin to reassess the benefit-risk balance of these medicines.

This review is being initiated further to information received from the French medicines agency on a long-term epidemiological study in patients treated during childhood with somatropin-containing medicines. The study results suggest an increased risk of mortality with somatropin therapy compared to the general population. The risk appears to be particularly increased when high doses are used (beyond doses as recommended in the Summary of Product Characteristics). The study looked at patients treated during childhood for growth hormone deficiency or short stature of unknown cause. Based on this observational study alone, the risk cannot be associated with certainty to the growth hormone treatment. The results need to be confirmed and complemented with further analyses.

Related information

- NutropinAq: EPAR
- Omnitrope: EPAR
- Valtropin: EPAR

Contact point:

Monika Benstetter or Sabine Haubenreisser
Tel. +44 (0)20 7418 8427
E-mail: press@ema.europa.eu

In summary, the SAGhE study reported an increased risk of death in patients who were treated with recombinant human growth hormone during childhood when compared to individuals in the general population of France. FDA is currently reviewing all available new information on this potential risk and at this time, recommends caution when interpreting the reported results. Additionally, FDA believes the benefits of recombinant growth hormone continue to outweigh the potential risks. Patients should continue to follow the advice of their healthcare provider. FDA will communicate with the public as soon as we have completed our evaluation. Further information is available in the European Medicines Agency (EMA) press releases[1,3] and the Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS) press release (in French).[2]

Long-Term Mortality after Recombinant Growth Hormone Treatment for Isolated Growth Hormone Deficiency or Childhood Short Stature: Preliminary Report of the French SAGhE Study

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Context: Little is known about the long-term health of subjects treated with GH in childhood, and Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) is a study addressing this question.

Objective: The objective of the study was to evaluate the long-term mortality of patients treated with recombinant GH in childhood in France.

Design: This was a population-based cohort study.

Setting: The setting of the study was a French population-based register.

Participants: A total of 6928 children with idiopathic isolated GH deficiency (n = 5162), neurosecretory dysfunction (n = 534), idiopathic short stature (n = 871), or born short for gestational age (n = 335) who started treatment between 1985 and 1996 participated in the study. Follow-up data on vital status were available in September 2009 for 94.7% of the patients.

Main outcome measures: All-cause and cause-specific mortality was measured in the study.

Results: All-cause mortality was increased in treated subjects [standardized mortality ratio (SMR) 1.33, 95% confidence interval (CI) 1.08–1.64]. In a multivariate analysis adjusted for height, the use of GH doses greater than 50 μg/kg · d was associated with mortality rates using external and internal references (SMR 2.94, 95% CI 1.22–7.07, hazard ratio 2.79, 95% CI 1.14–6.82). All type cancer-related mortality was not increased. Bone tumor-related mortality was increased (SMR 5.00, 95% CI 1.01–14.63). An increase in mortality due to diseases of the circulatory system (SMR 3.07, 95% CI 1.40–5.83) or subarachnoid or intracerebral hemorrhage (SMR 6.66, 95% CI 1.79–17.05) was observed.

Conclusions: Mortality rates were increased in this population of adults treated as children with recombinant GH, particularly in those who had received the highest doses. Specific effects were detected in terms of death due to bone tumors or cerebral hemorrhage but not for all cancers. These results highlight the need for additional studies of long-term mortality and morbidity after GH treatment in childhood. (*J Clin Endocrinol Metab* 97: 416–425, 2012)

Carel *et al.* Mortality after GH Treatment *J Clin Endocrinol Metab*, February 2012, 97(2):416–425

SAGhE

- ***S***afety and ***A***ppropriateness of ***GH*** treatments in ***E***urope
- A large study aiming to evaluate the long-term health of ~ 30,000 pts treated with rGH during childhood in the 1980s and 1990s in 8 European countries –Belgium, France, Germany, Italy, The Netherlands, Sweden, Switzerland, and UK– as a means of assessing the long-term safety of childhood GH treatment.
- Prespecified hypotheses of the study concerned all-cause and cancer related mortality.

Carel *et al.* Mortality after GH Treatment *J Clin Endocrinol Metab*, February 2012, 97(2):416–425

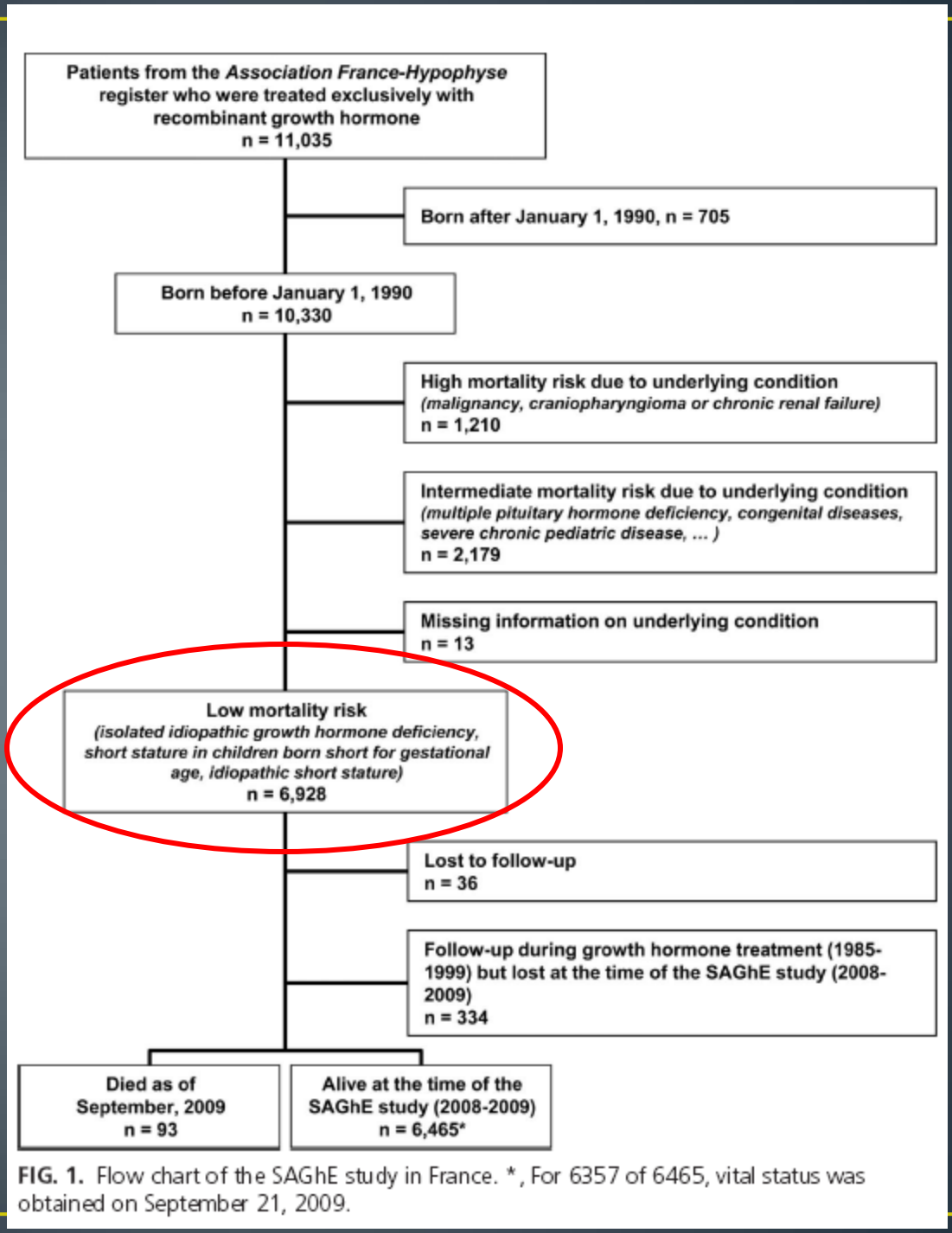

FIG. 1. Flow chart of the SAGhE study in France. *, For 6357 of 6465, vital status was obtained on September 21, 2009.

Data collection

- Data were routinely collected at baseline and at regular f/u visits and from ped endocrinologists until 1996 when the national compulsory register was disbanded.
- Additional follow-up data on GH treatment were collected from clinical centers in 2008–2010.
- Information on vital status was collected from two national sources of data.
- Cause of deaths were obtained from death certificates.

Carel *et al.* Mortality after GH Treatment *J Clin Endocrinol Metab*, February 2012, 97(2):416–425

SMR – Standardized Mortality Rate

TABLE 3. Adjusted SMR of GH-treated patients: final Poisson regression model

	SMR	(95% CI)
Mean GH dose: 0–20 μg/kg · d	1.00	
Mean GH dose: 20–30 μg/kg · d	0.95	(0.58–1.57)
Mean GH dose: 30–50 μg/kg · d	1.34	(0.52–3.43)
Mean GH dose: >50 μg/kg · d	2.94	(1.22–7.07)
Height at initiation of treatment ≥−2 SDS	1.00	
Height at initiation of treatment: −2 to −3 SDS	1.62	(0.69–3.84)
Height at initiation of treatment: <−3 SDS	2.31	(0.96–5.59)

Mean f/u time from treatment initiation to death or loss to f/u or census was 17.3 ± 4.1 yr

Carel *et al.* Mortality after GH Treatment *J Clin Endocrinol Metab*, February 2012, 97(2):416–425

Conclusion

- Despite the low statistical power of the study due to the low frequency of events, it detected an increase in mortality in a population of short children treated with rGH.
- High GH dose, > 50 ug/kg/d, was consistently associated with increased mortality in analyses with both internal and external references.

Carel *et al.* Mortality after GH Treatment *J Clin Endocrinol Metab*, February 2012, 97(2):416–425

TABLE 5. SMR by *International Classification of Diseases*, Ninth Revision (ICD-9) category and selected causes of death

	Observed	Expected	SMR	(95% CI)
ICD-9 categories				
Infectious and parasitic diseases (001–139)	3	1.05	2.86	(0.57–8.35)
Neoplasms (140–239)	7	6.89	1.02	(0.41–2.09)
Endocrine, nutritional, and metabolic diseases and immunity disorders (240–279)	2	0.31	6.50	(0.73–23.46)
Diseases of the blood and blood-forming organs (280–289)	1	0.88	1.13	(0.01–6.30)
Mental disorders (290–319)	1	1.32	0.75	(0.01–4.20)
Diseases of the nervous system and sense organs (320–389)	3	2.71	1.11	(0.22–3.24)
Diseases of the circulatory system (390–459)	9	2.93	3.07	(1.40–5.83)
Diseases of the respiratory system (460–519)	2	1.08	1.85	(0.21–6.66)
Diseases of the digestive system (520–579)	0	0.48		
Diseases of the genitourinary system (580–629)	0	0.02		
Complications of pregnancy, childbirth, and the puerperium (630–676)	0	0.14		
Diseases of the skin and sc tissue (680–709)	0	0.12		
Diseases of the musculoskeletal system and connective tissue (710–739)	0	0.09		
Congenital abnormalities (740–759)	0	0.01		
Certain conditions originating in the perinatal period (760–779)	1	1.14	0.88	(0.01–4.90)
Symptoms, signs, and ill-defined conditions (780–799)	21[a]	6.28	3.35	(2.07–5.11)
Injury and poisoning (800–999)	43	44.22	0.97	(0.70–1.31)
Neoplasms (140–239)	7	6.89	1.02	(0.41–2.09)
Malignant neoplasm of lymphatic and hematopoietic tissue (200–208)	2	1.36	1.47	(0.17–5.31)
Malignant neoplasm of bone and articular cartilage (170)	3	0.60	5.00	(1.01–14.61)
All other neoplasms[b]	2	4.93	0.41	(0.05–1.46)
Diseases of the circulatory system (390–459)	9	2.93	3.07	(1.40–5.83)
Other disorders of circulatory system (390–409. 415–419. 424. 439–459)	1	0.66	1.53	(0.02–8.49)
Other heart diseases (420–423. 425–429)	4	1.19	3.37	(0.91–8.64)
including cardiomyopathy and cardiomegaly (425. 429.3)	2	0.28	7.11	(0.80–25.67)
Cerebrovascular disease (430–438)	4	0.76	5.29	(1.42–13.55)
including subarachnoid hemorrhage, intracerebral hemorrhage and other non-traumatic intracranial hemorrhages (430–432)	4	0.60	6.66	(1.79–17.05

[a] Includes five deaths that occurred abroad, for which the cause of death is not available.

[b] The two cases of fatal neoplasms observed were a malignant neoplasm of the lip, oral cavity, and pharynx (140–149) and a malignant melanoma of the skin (172).

Conclusion

- No increase in cancer-related deaths overall was detected.
- Specific effects on death associated with bone tumors and cerebrovascular diseases were detected.
- Results do not allow the conclusion of the causal role of GH treatment in the findings but *highlight the need for additional studies on long-term morbidity and mortality after GH treatment in childhood, in particular when high doses have been used*.

Carel *et al.* Mortality after GH Treatment *J Clin Endocrinol Metab*, February 2012, 97(2):416–425

Long-Term Mortality and Causes of Death in Isolated GHD, ISS, and SGA Patients Treated with Recombinant Growth Hormone during Childhood in Belgium, The Netherlands, and Sweden: Preliminary Report of 3 Countries Participating in the EU SAGhE Study

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Context: The long-term mortality in adults treated with recombinant GH during childhood has been poorly investigated. Recently released data from the French part of the European Union Safety and Appropriateness of GH treatments in Europe (EU SAGhE) study have raised concerns on the long-term safety of GH treatment.

Objective: To report preliminary data on long-term vital status and causes of death in patients with isolated GH deficiency or idiopathic short stature or born small for gestational age treated with GH during childhood, in Belgium, The Netherlands, and Sweden.

Design: Data were retrieved from national registries of GH-treated patients and vital status from National Population Registries. Causes of death were retrieved from a National Cause of Death Register (Sweden), Federal and Regional Death Registries (Belgium), or individual patient records (The Netherlands).

Patients: All patients diagnosed with isolated GH deficiency or idiopathic short stature or born small for gestational age started on recombinant GH during childhood from 1985–1997 and who had attained 18 yr of age by the end of 2010 were included. Vital status was available for approximately 98% of these 2,543 patients, corresponding to 46,556 person-years of observation.

Main Outcome Measure: Vital status, causes of death, age at death, year of death, duration of GH treatment, and mean GH dose during treatment were assessed.

Results: Among 21 deaths identified, 12 were due to accidents, four were suicides, and one patient each died from pneumonia, endocrine dysfunction, primary cardiomyopathy, deficiency of humoral immunity, and coagulation defect.

Conclusions: In these cohorts, the majority of deaths (76%) were caused by accidents or suicides. Importantly, none of the patients died from cancer or from a cardiovascular disease. (*J Clin Endocrinol Metab* 97: E213–E217, 2012)

Long-Term Mortality and Causes of Death in Isolated GHD, ISS, and SGA Patients Treated with rGH during Childhood in Belgium, The Netherlands, and Sweden

TABLE 1. Patient distribution and underlying diagnoses in GH-treated patients evaluated for vitality

Country	No. of patients		Percent in low-risk group	No. of patients			Person-years of observation in low-risk group (on/off GH treatment)	Vital status information available (%)
	Total cohort	Low-risk group		IGHD	ISS	SGA		
Belgium	980	374	38.2	237	94	43	7512 (2268/5244)	97.0
The Netherlands	1348	484	35.9	205	115	164	8475 (3092/5383)	97.8
Sweden	2971	1685	56.7	1224	343	118	30,569 (10,913/19,656)	98.4

N = 2,543

Sävendahl *et al*. Mortality after Childhood GH Therapy *J Clin Endocrinol Metab*, February 2012, 97(2):E213–E217

TABLE 3. Characteristics of individual patients treated with recombinant GH during childhood who died during follow-up

Patient	Country	Diagnosis	Gender	Duration of GH treatment (yr)	Mean GH dose (mg/kg · d)	Age at death (yr)	Year of death	Cause of death
1	Belgium	IGHD	M	3.2	0.035	24.8	2005	Traffic accident, pedestrian
2	Belgium	IGHD	F	4.0	0.029	19.4	1994	Homicide, fire arm
3	Belgium	IGHD	M	4.9	0.028	23.7	2000	Traffic accident, car occupant
4	Netherlands	IGHD	M	4.6	0.028	27.4	2002	Pneumonia
5	Netherlands	SGA	M	7.8	0.054	16.8	2000	Traffic accident, run over
6	Sweden	IGHD	M	12.8	0.033	22.1	2006	Suicide, poisoning
7	Sweden	IGHD	F	3.4	0.036	29.8	2007	Other endocrine dysfunction
8	Sweden	IGHD	F	1.6	0.027	28.8	2005	Poisoning, unclear if purposeful
9	Sweden	IGHD	M	1.9	0.033	19.3	1995	Primary cardiomyopathy
10	Sweden	IGHD	F	2.3	0.033	18.5	1995	Traffic accident, pedestrian
11	Sweden	IGHD	M	2.0	0.034	26.9	2002	Poisoning, unclear if purposeful
12	Sweden	IGHD	M	1.3	0.031	12.2	1994	Poisoning, unclear if purposeful
13	Sweden	IGHD	M	0.4	0.036	33.5	2010	Poisoning, unclear if purposeful
14	Sweden	IGHD	M	11.4	0.033	18.9	2008	Suicide, hanging
15	Sweden	IGHD	M	1.0	0.030	12.2	1997	Deficiency of humoral immunity
16	Sweden	IGHD	M	4.7	0.048	31.0	2009	Accident, due to legal intervention
17	Sweden	ISS	M	4.9	0.034	30.5	2005	Coagulation defect
18	Sweden	ISS	M	11.3	0.033	27.6	2008	Accident, drowning
19	Sweden	ISS	M	10.7	0.033	17.9	2007	Suicide, hanging
20	Sweden	ISS	M	3.5	0.033	14.0	1999	Traffic accident, collision
21	Sweden	ISS	M	5.5	0.033	21.5	2001	Suicide, unspecified

F, Female; M, male.

Sävendahl *et al*. Mortality after Childhood GH Therapy *J Clin Endocrinol Metab*, February 2012, 97(2):E213–E217

Long-Term Mortality and Causes of Death in Isolated GHD, ISS, and SGA Patients Treated with rGH during Childhood in Belgium, The Netherlands, and Sweden

- Majority of deaths (16/21) were caused by accidents or suicides.
- Suicide is well known to be one of the most common causes of death in this age group.
- Thus, it isn't surprising that 4/ 21 deaths were suicides.
- Of the 5 pts who died from an underlying disorder, no death was caused by cancer or CVD, and none of these pts were treated with a daily GH dose > 36 ug/kg/d.
- SMR were not calculated because the total number of pts was still relatively low.

Sävendahl *et al*. Mortality after Childhood GH Therapy *J Clin Endocrinol Metab*, February 2012, 97(2):E213–E217

Controversial issues

Carel's study is the first to find that persons treated with GH had a higher incidence of CVA events.

- Acromegalics are at higher risk of CVA deaths, w/ those that received radiotherapy as treatment at highest risk.
- Those with hypopituitarism are also at higher risk for CVA deaths, thus it is unknown whether the increased risk seen in acromegaly is due to the GH disturbance or the oft associated hypopituitarism.
- Not seen in other countries participating in SAGhE.

DiVall SA & Radovick. GH and treatment controversy; long-term safety of rGH. *Curr Pediatr Rep*. 2013, 1:128-132.

Controversial issues

Markers of GH efficacy, such as adult height or estimated height gain, were not reported.

- Evaluation of data from a risk/benefit perspective could not be done.
- Adult ht data on a smaller cohort of the French pts were published earlier, and indicated that adult ht in pts taking GH until adult height was not significantly different from pts who ended treatment before the epiphyses were closed, putting into question the efficacy of GH and/or the accuracy of the diagnosis of GHD.

DiVall SA & Radovick. GH and treatment controversy; long-term safety of rGH. *Curr Pediatr Rep*. 2013, 1:128-132.

Controversial issues

The manner in which these data were released and shared with the GH prescribing community was not typical and caused some consternation.

- Press releases were posted 14 months before a publication with data became available.
- The medical community was left with scanty information to share with their patients and put up with the burden of uncertainty.

DiVall SA & Radovick. GH and treatment controversy; long-term safety of rGH. *Curr Pediatr Rep*. 2013, 1:128-132.

Response of providers

- Results of the French study have not significantly changed prescribing practices.
- Providers that are rigorous in their diagnosis of GH deficiency and conservative in prescribing GH continue to be so, citing the French study and other possible unknown risks.
- Providers who use a broader criterion for the diagnosis of GH deficiency and are more liberal in their prescribing practices of GH cite the excellent safety profile with decades of use and the limitations of the study.

DiVall SA & Radovick. GH and treatment controversy; long-term safety of rGH. *Curr Pediatr Rep*. 2013, 1:128-132.

Response of providers

- Practitioners have the obligation to understand the limitations of the data and present the rationale for GH therapy to pts in a nonbiased manner.
- We present the benefits of GH and the commitment that therapy requires.
- GH therapy improves stature but many years of therapy are needed for maximal benefit.
- GH treatment continuation in those with adult GH deficiency is a possibility, --costs of treatment to third party payers is high, and that contact w/ physicians for therapy monitoring is frequent-- at least 3 times yearly.

DiVall SA & Radovick. GH and treatment controversy; long-term safety of rGH. *Curr Pediatr Rep*. 2013, 1:128-132.

Response of providers

- Risks of GH therapy - we review the excellent safety record of GH use, the known side effects, including minimal pain at the injection site, rare occurrences of increased intracranial pressure, SCFE, scoliosis progression, edema, and pancreatitis.
- We present GH as a growth promoting agent with theoretical risks of increasing cancer and diabetes, and emphasize that there is no conclusive evidence of an increased cancer or diabetes risk in patients receiving GH.

DiVall SA & Radovick. GH and treatment controversy; long-term safety of rGH. *Curr Pediatr Rep*. 2013, 1:128-132.

Response of providers

- In discussing the new data with patients, we mention the studies and the increased risk of cerebrovascular disease in one patient population but not the others, and the strengths and criticisms of the study.

DiVall SA & Radovick. GH and treatment controversy; long-term safety of rGH. *Curr Pediatr Rep*. 2013, 1:128-132.

ARTICLES

Growth hormone treatment for childhood short stature and risk of stroke in early adulthood

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ABSTRACT

Objectives: We investigated the incidence of stroke and stroke subtypes in a population-based cohort of patients in France treated with growth hormone (GH) for short stature in childhood.

Methods: Adult morbidity data were obtained in 2008–2010 for 6,874 children with idiopathic isolated GH deficiency or short stature who started GH treatment between 1985 and 1996. Cerebrovascular events were validated using medical reports and imaging data and classified according to standard definitions of subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke. Case ascertainment completeness was estimated with capture-recapture methods. The incidence of stroke and of stroke subtypes was calculated and compared withpopulation values extracted from registries in Dijon and Oxford, between 2000 and 2012.

Results: Using both Dijon and Oxford population-based registries as references, there was a significantly higher risk of stroke among patients treated with GH in childhood. The excess risk of stroke was mainly attributable to a very substantially and significantly higher risk of hemorrhagic stroke (standardized incidence ratio from 3.5 to 7.0 according to the registry rates considered, and accounting or not accounting for missed cases), and particularly subarachnoid hemorrhage (standardized incidence ratio from 5.7 to 9.3).

Conclusions: We report a strong relationship between hemorrhagic stroke and GH treatment in childhood for isolated growth hormone deficiency or childhood short stature. Patients treated with GH worldwide should be advised about this association and further studies should evaluate the potentially causal role of GH treatment in these findings. *Neurology*® 2014;83:780–786

GLOSSARY

CI = confidence interval; GH = growth hormone; ICD-10 = *International Classification of Diseases*, tenth revision; ICH = intracerebral hemorrhage; IS = ischemic stroke; SAGhE = Safety and Appropriateness of Growth hormone treatments in Europe; SAH = subarachnoid hemorrhage; SIR = standardized incidence ratio.

Little information is available about the long-term outcome after growth hormone (GH) treatment, particularly in individuals who received treatment in childhood.[1] Because of the mitogenic and proliferative properties of GH, most attention has focused on the risk of cancer after GH treatment.[2,3] The Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) project is a multinational European study that aims to evaluate long-term mortality and cancer morbidity in subjects who were treated with GH in childhood. A preliminary report

Conclusions: We report a strong relationship between hemorrhagic stroke and GH treatment in childhood for isolated growth hormone deficiency or childhood short stature. Patients treated with GH worldwide should be advised about this association and further studies should evaluate the potentially causal role of GH treatment in these findings. *Neurology*® 2014;83:780–786

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Supplemental data at Neurology.org

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Dear PES members,

PES Pediatric Endocrine Society

Recently, there has been significant media attention and public distress due to a publication in the journal, Neurology (August 26, 2014, Vol 83, PMID: 25122206), that described a possible association between GH therapy during childhood and stroke in early adulthood[1]. The PES Board of Directors and members of the Drug and Therapeutics (D&T) Committee have carefully analyzed the article and collectively configured this response to address the concerns in the community that we serve. PES is working closely with other major Societies including the Endocrine Society and the Growth Hormone Research Society to provide a timely, collaborative editorial response to Poidvin *et al.*[1], and the accompanying editorial by Dr. Ichord[2] We hope that this message will be helpful to alleviate any anxiety and distress among patients, families, and medical providers regarding the safety of GH therapy.

These recent reports raise concerns about a potential relationship between GH treatment during childhood among "low-risk" patients (isolated GH deficiency, idiopathic short stature, and small for gestational age) and increased risk for stroke (both hemorrhagic and ischemic stroke) in young adulthood. In this study, 11 out of the 6,874 GH recipients had a fatal or non-fatal stroke. There are several significant limitations to this study that deeply concern the pediatric endocrine community across the world and necessitate caution in interpreting the conclusions.

In conclusion, the PES BOD and D&T Committee members believe that, despite the concerns raised by the article and editorial in the journal, Neurology, GH therapy can continue to be safely administered to children who would benefit from it. Any concern about GH therapy and long-term stroke risk cannot be validated at this time until further rigorous studies are done. In addition, there is no current evidence of a need for cardiovascular surveillance or preventive strategies in adults who received GH therapy in childhood.

ENDOCRINE SOCIETY

Hormone Science to Health

Endocrine Society Statement on Possible Association Between GH Therapy in Childhood and Later Stroke

August 25, 2014

A just published study in Neurology described a possible association between growth hormone (GH) therapy during childhood among "low risk patients" (isolated GH deficiency, idiopathic short stature and small for gestational age) and increased risk for stroke (both hemorrhagic and ischemic stroke) in young adulthood in France[1]. The study found that 11 out of the 6,874 GH recipients had a fatal or non-fatal stroke. While this raises some concerns, there are several significant limitations to this study identified by experts from the Society, Pediatric Endocrine Society, and Growth Hormone Research Society that necessitate caution in interpreting the conclusions.

Data for cause of death in those individuals (4 out of 11) who had fatal stroke were obtained from the French Death Certificates. Death certificates in France may not reflect the underlying (proximate) cause of death because they document only the immediate symptom prior to death. A review of medical records, a much more accurate way to determine the cause of death, is the preferred method of ascertaining cause and would give more credence to the conclusions.

There may have been significant ascertainment bias of the cases since the data were obtained from mailed questionnaires which had a low (45%) response rate. There is lack of adjustment for the other major risk factors for stroke such as hypertension, diabetes, obesity, smoking/alcohol, and family history of stroke; and the lack of sufficient detail about GH therapy (e.g., dose and duration of therapy, interval between treatment and event, and age at the time of the event) in 4 of the 11 patients. Given the low numbers for incidence of stroke in this cohort, any small change in the observed rates could potentially significantly alter the analyses and results.

Perhaps most importantly, the two control groups that were used to compare estimated stroke rates in the cohort were from a general population and one of the two control groups was from a different country (United Kingdom). A suitable cohort for comparison might have been untreated French adults of the same age and size with the same diagnoses since untreated adult GH deficiency itself is a risk factor for cardiovascular disease and short stature itself has been associated with adverse cardiovascular outcomes. The elevated mortality rate observed in the shortest subjects (at initiation of treatment)

seems to reinforce the contention that some element of the underlying condition which imparted this increased risk, rather than the treatment, *per se* was the culprit.

Of note is that the same group concluded that there was an association between childhood GH therapy for low risk indications and mortality risk in adulthood in 2012[3]. This was contradicted by a concurrent publication in which co-investigators in that study reported a very low mortality rate due to diseases of the circulatory system with no deaths due to diseases of the circulatory system in "low risk" individuals in Belgium, the Netherlands and Sweden. In addition, the U.S. Food and Drug Administration "identified a number of study design weaknesses that limit the interpretability of the study results" making "the evidence regarding recombinant hGH and increased risk of death is inconclusive" [5].

The Endocrine Society believes that until rigorously performed studies are done which confirm the Poidvin et al's observations, GH therapy can continue to be safely administered to children who would benefit from it. In addition, there is no current evidence of a need for cardiovascular surveillance or preventive strategies in adults who received growth hormone therapy in childhood. In addition, the Endocrine Society discourages patients from stopping their GH therapy without discussing the risks and benefits with their physician.

1. Poidvin A, Touzé E, Ecosse E, Landier F, Béjot Y, Giroud M, Rothwell PM, Carel JC, Coste J. Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. Neurology. 2014 Aug 13
2. Ichord, RN.Adult stroke risk after growth hormone treatment in childhood. First do no harm. Neurology 2014;83:776–777
3. Carel JC, Ecosse E, Landier F, Meguellati-Hakkas D, Kaguelidou F, Rey G, Coste J. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. J Clin Endocrinol Metab 2012;97:416-425
4. Sävendahl L, Maes M, Albertsson-Wikland K, Borgström B, Carel JC, Henrard S, Speybroeck N, Thomas M, Zandwijken G, Hokken-Koelega A. Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study. J Clin Endocrinol Metab 2012;97:E213-217
5. FDA Drug Safety Communication: Safety review update of Recombinant Human Growth Hormone (somatropin) and possible increased risk of death: http://www.fda.gov/Drugs/DrugSafety/ucm265865.htm.

Endocrine Society - rGH

- The Endocrine Society believes that until rigorously performed studies are done which confirm the Poidvin et al's observations, GH therapy can continue to be safely administered to children who would benefit from it.
- In addition, there is no current evidence of a need for cardiovascular surveillance or preventive strategies in adults who received growth hormone therapy in childhood.
- In addition, the Endocrine Society discourages patients from stopping their GH therapy without discussing the risks and benefits with their physician.

Current FDA GH indications

Indications for Growth Hormone Therapy	
Growth hormone deficiency	Prader-Willi syndrome
Idiopathic short stature	Noonan syndrome
Born small for gestational age	Short bowel
Turner syndrome	AIDS wasting
Chronic renal insufficiency	Adult GHD

SUMMARY

- Recombinant growth hormone therapy has had an exemplary track record of safety and efficacy.
- However, several studies have shown that the therapy carries risks of long-term morbidities, some unexplained.
- Hence, we believe practitioners who prescribe rGH be provided with solid data regarding the long-term safety issues and patients be adequately informed of the benefits and risks related to therapy.

QUESTIONS?