# 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

Lars Sävendahl, Marc Maes, Kerstin Albertsson-Wikland, Birgit Borgström, Jean-Claude Carel, Séverine Henrard, Niko Speybroeck, Muriel Thomas, Gladys Zandwijken, and Anita Hokken-Koelega

Division of Pediatric Endocrinology (L.S.), Department of Women's and Children's Health, Karolinska Institutet, SE-171 76 Stockholm, Sweden; Department of Clinical Science, Intervention, and Technology (B.B.), Karolinska Institutet, SE-141 86 Stockholm, Sweden; Division of Pediatric Endocrinology (M.M.), Department of Pediatrics, Cliniques Universitaires St. Luc; Institut de Recherche Santé et Société (S.H., N.S.), Université Catholique de Louvain, Brussels 1200, Belgium; and Belgian Study Group for Pediatric Endocrinology (M.M., M.T.), Brussels 1090, Belgium; Göteborg Pediatric Growth Research Center (K.A.-W.), Institute of Clinical Sciences, The Sahlgrenska Academy at University of Gothenburg, SE-416 85 Gothenburg, Sweden; Department of Paediatric Endocrinology and Diabetology (J.-C.C.), Institut National de la Santé et de la Recherche Médicale CIC-EC5 and Centre de Référence des Maladies Endocriniennes Rares de la Croissance, Assistance Publique-Hôpitaux de Paris Robert Debré Hospital and University Paris-Diderot, F-75019 Paris, France; Dutch Growth Research Foundation (G.Z., A.H.-K.), 3016 AH Rotterdam, The Netherlands; and Department of Pediatrics (A.H.-K.), Division of Endocrinology, Erasmus Medical Center, 3015 CE Rotterdam, The Netherlands

**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**)

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Abbreviations: IGHD, Isolated GH deficiency; ISS, idiopathic short stature; SAGhE, Safety and Appropriateness of Growth Hormone Treatments in Europe; SGA, small for gestational age.

Recombinant GH has been used for more than 25 yr. Despite this, the long-term mortality in patients treated with GH during childhood has been poorly investigated. In an era when GH is increasingly used to treat short stature in non-GH-deficient children, the long-term safety should be monitored closely. So far knowledge regarding long-term safety of GH has been restricted to patients followed in large postmarketing databases where data have been collected only during and shortly after treatment (1, 2). In addition, the voluntary data collection of these databases renders them incomplete and therefore prone to selection biases (3). To fill this lack of knowledge, a collaborative effort [Safety and Appropriateness of Growth Hormone Treatments in Europe (SAGhE)] is currently ongoing in Europe involving eight countries: Belgium, France, Germany, Italy, The Netherlands, Sweden, Switzerland, and The United Kingdom. A recent release of preliminary data from France showed an increased overall mortality in adults treated with recombinant GH during childhood for isolated GH deficiency (IGHD), idiopathic short stature (ISS), and born small for gestational age (SGA) (4, 5). These data have caused concerns and have highlighted the importance of the efforts undertaken by the SAGhE consortium to assess the long-term safety of GH therapy. Because information on vital status and causes of death has now become available in Belgium, The Netherlands, and Sweden, we considered it important to present these data to complement those obtained in France. Due to lack of statistical power, however, calculations of standardized mortality ratios were not performed.

## Subjects and Methods

Patients being started on recombinant GH treatment during childhood between 1985 and 1997, irrespective of treatment duration, and who had attained 18 yr of age by the end of year 2009 (The Netherlands) or the end of year 2010 (Belgium and Sweden) were included. Patients who had been treated with pituitary-derived GH were excluded. To identify patients in a nonbiased manner, national registries in Belgium, The Netherlands, and Sweden encompassing in principle all patients treated with recombinant GH during childhood were used. In addition, patients diagnosed with IGHD (Sweden) or ISS (Belgium and Sweden) or born SGA (Belgium, The Netherlands and Sweden) who had been treated with recombinant GH within clinical trials were included.

To ensure a correct risk classification, the underlying diagnoses recorded in each national registry were verified from patient records by registry monitors. After completed verification of diagnoses, all GH-treated patients were categorized in three risk groups. Patients were placed in the high-risk group if they had been treated for cancer, craniopharyngioma, or chronic renal failure. Intermediate risk was defined as treatment with GH in the context of multiple pituitary hormone deficiency (GH and at least one other pituitary hormone deficiency) or treatment in the context of defined pediatric syndromes (such as the Turner, Noonan, neurofibromatosis type 1, Prader-Willi, and Fanconi syndromes) known to be associated with an increased risk of mortality or, in the context of benign pituitary tumors, severe craniofacial or other malformations, or severe pediatric chronic diseases. Low risk was defined as treatment for IGHD, ISS, and SGA without syndrome or genetic defects. Patients in the low-risk group were selected for this study.

Information about baseline patient characteristics and treatment was collected from the national GH registries. Vital status data were obtained from the National Population Registry in each country. The cause of death was retrieved from a National Cause of Death Registry (Sweden) or from the Federal and the three Regional Death Registries (Belgium) or individual patient records (The Netherlands). A census date of December 31, 2010, was set. The study was approved by the ethical committees or institutional review boards in accordance with local rules in the three countries.

### Statistical analysis

Person-years of observation were calculated from the date of first administration of GH up to the date of death or loss to follow-up or December 31, 2010. The mean GH dose was calculated by dividing the total amount of GH administered by the number of days of childhood treatment.

## Results

Altogether in Belgium, The Netherlands, and Sweden, 5299 children were confirmed to have started treatment with recombinant GH from 1985–1997. Among these patients, 2543 (48.0%) were diagnosed with IGHD, ISS, or SGA and classified as low-risk for long-term mortality. The proportion of low-risk patients in the different cohorts of GH-treated patients varied between the three countries being highest in Sweden (56.7%) and lowest in The Netherlands (35.9%). Among low-risk patients, 1666 (65.5%) were diagnosed with IGHD, 552 (21.7%) with ISS, and 325 (12.8%) with SGA. The distribution of diagnoses differed between the countries as detailed in Table 1. Analyses of gender distribution showed that 814 (32.0%) were females and 1729 (68.0%) were males. The distribution of GH dosing in the low-risk group is detailed in Table 2. The majority of patients were treated with GH doses ranging from 0.030–0.050 mg/kg · d. In the SGA group, a relatively greater proportion of patients was treated with GH doses exceeding 0.050 mg/kg · d.

Information about vital status was available for approximately 98% of the subjects, a figure that only slightly varied between the three countries (Table 1). The total number of person-years of observation was 46,556:

**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 |

16,273 person-years on GH treatment and 30,283 person-years after GH treatment. At census date (December 31, 2010), the mean age of all living patients was 28.3 yr in Sweden, 29.4 yr in Belgium, and 27.2 yr in The Netherlands.

Of the 2543 low-risk patients, 21 (four females and 17 males) had died before the census date of December 31, 2010 (Table 3). Of these 21 deceased individuals, 15 had been diagnosed with IGHD, five with ISS, and one with SGA. In deceased subjects, the duration of GH treatment varied from 0.4–12.8 yr and the mean GH dose from 0.027–0.054 mg/kg · d.

As detailed in Table 3, the majority of deaths were caused by an accident (n = 12) or suicide (n = 4). One patient each died from pneumonia, endocrine dysfunction, primary cardiomyopathy, deficiency of humoral immunity, and coagulation defect. Two of the deceased patients (patients 5 and 16) were treated with relatively high mean doses of GH (0.054 and 0.048 mg/kg · d, respectively). Both deaths were attributed to accidents unlikely to be linked to their previous GH treatment.

## Discussion

In this preliminary report, vital status was confirmed in approximately 98% of all individuals who during childhood were diagnosed with IGHD, ISS, or SGA and started on GH treatment from 1985–1997 in Belgium, The Netherlands, and Sweden. Patients were identified through national registries, encompassing most of the patients who received GH during childhood in this time period, thereby minimizing any selection bias. All diagnoses were verified with the treating physicians/clinics or patient records, and therefore misclassification is unlikely. The cause of death could be obtained in all patients.

**TABLE 2.** Distribution of GH dosing

| Mean dose (mg/kg · d) | IGHD | ISS | SGA | Total (low-risk group) |
|---|---|---|---|---|
| <0.020 | 36 | 9 | 4 | 49 |
| 0.020–0.030 | 318 | 98 | 28 | 444 |
| 0.030–0.050 | 1238 | 331 | 136 | 1705 |
| >0.050 | 71 | 113 | 157 | 341 |
| Missing information | 3 | 1 | 0 | 4 |

The majority of deaths (16 of 21, 76%) were caused by accidents or suicides. Suicide is well known to be one of the most common causes of death in this age group. It is therefore not surprising that four of 21 deaths (19%) were caused by suicides. The cohort of studied patients consisted of 68% males, whereas among the deaths, 81% (17 of 21) were males. Taking into account the well-known higher mortality rate in young males, the ratio of males to females among the 21 deaths is not unexpected.

Of the five patients who died from an underlying disorder, no death was caused by cancer or cardiovascular disease, and none of these patients were treated with a daily GH dose exceeding 0.036 mg/kg. Our findings contrast with recently released data from France suggesting increased mortality rates for bone tumors and cardiovascular events (4, 5). These apparent differences could be due to differences in the power of the different parts of the European Union (EU) SAGhE study or to differences in the types of patients treated in various countries; selections of patients for the studies; proportions of IGHD, ISS, and SGA; dose ranges of GH; duration of follow-up; or completeness of data.

Despite the fact that all patients treated with GH during childhood were included, we decided not to calculate standardized mortality ratios because the total number of patients is still relatively low. Indeed, very large numbers are needed for evaluation of cause-specific mortality, which can be achieved only by extensive international collaborations. Such a collaborative effort is currently ongoing in Europe within EU SAGhE, involving the three countries in this paper as well as France, Germany, Italy, the United Kingdom, and Switzerland.

Given the concerns raised by the dissemination of the data from France, we considered it worth reporting preliminary data on long-term mortality and causes of death as they became available in Belgium, The Netherlands, and Sweden. Although we do not dispute the veracity of the data reported from France, we did not observe a similar distribution of causes of death; not a single case of death related to cancer or cardiovascular disease was identified. Altogether, the results stress the importance of stud-

**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.

ies of long-term outcomes after childhood treatments and highlight the importance of the EU SAGhE study and the need for similar studies to be performed elsewhere. All partners are more than ever committed to achieve this ambitious but difficult task and to convey the results of the EU SAGhE study to the wider community, which can be expected within 2 yr.

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Address all correspondence and requests for reprints to: Lars Sävendahl, Division of Pediatric Endocrinology, Karolinska University Hospital Q2:08, SE-171 76 Stockholm, Sweden. E-mail: lars.savendahl@ki.se.

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Disclosure Summary: B.B., S.H., N.S., M.T., and G.Z. have nothing to declare. L.S., M.M., K.A.-W., J.-C.C., and A.H.-K. have conflicts of interest to declare, all outside the scope of the submitted work; L.S. is a member of the NordiNet International Study Committee (Novo), recipient of investigator-initiated independent research grants from Novo Nordisk and Pfizer and lecture fees from Novo Nordisk, Pfizer, Ipsen, Sandoz, and MerckSerono; M.M. received lecture fees from Novo Nordisk and Lilly; K.A.-W. received investigator-initiated independent research grants from Pfizer, Novo Nordisk, Ipsen, and MerckSerono; J.-C.C. is an investigator in clinical trials using GH sponsored by Pfizer and Lilly and in postmarketing studies using several brands of GH, is a member of the French advisory board of the KIGS postmarketing study (Pfizer), and has received support for travel to international meetings from several GH manufacturers; A.H.-K. is a member of the KIGS Advisory Board and recipient of investigator-

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