Final Report Summary - SAGHE (Safety and Appropriateness of Growth hormone treatments in Europe)

Recombinant growth hormone is used in children since 1985. Current indications for growth hormone include growth hormone deficiency and an increasing number of conditions where childhood short stature is not primarily due to deficient endogenous growth hormone secretion. Mean treatment durations are increasing. Although the long-term efficacy of growth hormone in children with severe growth hormone deficiency is undisputed, these patients represent a limited proportion of those treated. In patients, with short stature due to other conditions, the effect of growth hormone has been poorly evaluated. In addition, the clinical significance of height gains remains uncertain and most quality of life evaluations have shown no benefit from growth hormone treatments.

Short-term safety of growth hormone (during treatment) is generally considered satisfactory and its evaluation is based on large samples of patients followed in post-marketing databases. In contrast, long term safety has been poorly evaluated and several signals raise the question of a long term oncogenic effect.

The objectives of SAGHE study are to address some of the questions raised and more specifically:

- to constitute a large meta-cohort of young adults treated with recombinant growth hormone in childhood from representative European Union (EU) countries;
- to evaluate the long-term results of treatment on height and their determinants;
- to evaluate the correlates of height gains with quality of life in young adults;
- to evaluate the long-term mortality and cancer morbidity and to compare it with the general population.

This information will be integrated with the current body of knowledge in the field and will be disseminated to the entire EU, in order to improve the clinical management and safety for children in the EU.

The study is organised around five work packages (WPs):

WP1: Long term efficacy of growth hormone after treatment in childhood
WP2: Long term mortality and its determinants in individuals treated with growth hormone in childhood
WP3: Long term cancer incidence and its determinants in individuals treated with growth hormone in childhood
WP4: Translating data obtained and currently available evidence into clinical practice recommendations on growth hormone use in children for European citizens
WP5: Management.

This second interim report provides information on the study progress and the final results. The main objectives during this period were:
- to finalise the establishment of the metacohort of patients. Altogether, the number of patients included is 25,587, which represents 88% of the initially expected number (29,000);
- to deliver WPs 1 to 4.

In WP1, we were able to perform the largest data collection ever performed on adult height and quality of life in young adults after growth hormone treatment in childhood. Close to 12,000 adult heights were recorded, 52% of those included. Quality of life could be studied in a large sample (7,400 patients) of GH-treated patients. Our preliminary results seem to confirm our recent publications on the analysis of QOL in the general population, where only extremely short individuals (below -4 SD) have a decreased QOL associated with short stature.

In WP2, two publications were produced so far, describing mortality in patients treated in France and in three additional countries (Belgium, the Netherlands, Sweden). These publications raise questions regarding long-term health in those who have been treated with GH but complete SAGHE data analysis and further work will be needed.

In WP3, data has been collected in the countries where a cancer database is available. In the other countries, additional work is being done to obtain a valid evaluation of cancer risk.

In WP4, a symposium at the next Joint Meeting of Pediatric Endocrinology, Milan, Italy, 19 September 2013 will be held to inform professionals of the results. In addition, a Growth Hormone Safety Workshop will be held in Manchester at the beginning of 2014.

Project context and objectives:

Overview of the objectives of the study

Recombinant growth hormone is used in children since 1985. Current indications for growth hormone include growth hormone deficiency and an increasing number of conditions where childhood short stature is not primarily due to deficient endogenous growth hormone secretion. Mean treatment durations are increasing. Although the long term efficacy of growth hormone in children with severe growth hormone deficiency is undisputed, these patients represent a limited proportion of those treated. In patients, with short stature due to other conditions, the effect of growth hormone has been poorly evaluated. In addition, the clinical significance of height gains remains uncertain and most quality of life evaluations have shown no benefit from growth hormone treatments.

Short-term safety of growth hormone (during treatment) is generally considered satisfactory and its evaluation is based on large samples of patients followed in post-marketing databases. In contrast, long term safety has been poorly evaluated and several signals raise the question of a long term oncogenic effect.

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Objectives of the study during the second period
1 December 2010 to 30 November 2012

Milestones:
M 1.2: Finalisation of the metacohort list of patients
M1.3: Mid-term project checked
M1.4: End of WP1, WP2, WP3 check
M4.1: Organisation of the tasks for WP4
M4.2: Final consortium meeting and end of the project
M4.2: All conclusions of all the project activities and final evaluation of the results
M4.2: Termination of the project dissemination and planning of new extra activities after the end of the project
M5.1: Project meeting reports every 12 months.

Deliverables:

D1: Long term efficacy of growth hormone after treatment in childhood
D2: Long term mortality and its determinants in individuals treated with growth hormone in childhood
D3: Long term cancer incidence and its determinants in individuals treated with growth hormone in childhood
D4: Integration of data and dissemination to users.

Project results:

One of major objective during this period was to finish to establish the metacohort of patients in each participating country. This objective pertains to WP1 and was pivotal to the accomplishment of WP2 and WP3. As stated in the grant annex 1 and in the first interim report, it is clear that there were differences in the state of preparedness of each country with regard to this task. For instance, as detailed below, some countries had pre-established national databases of growth hormone treated patients, whereas others had to constitute one as part of SAGHE. During this second period, we were able to establish the cohort of patients in all countries with a tremendous improvement compared to the first period particularly in United Kingdom, Italy, Germany and Switzerland.

On this basis we have been able to achieve the study and to deliver results for each WP. Three meetings have been organised to follow the progression of the study. All data have been cleaned locally. Then data have been reviewed and if necessary cleaned again by the WP leader in charge of his corresponding WP.

Work progress and achievements during the period for each WP

Since the WPs are defined as unified tasks resulting from the individual actions of each partner from individual countries, the progress for each WP will be presented both globally and for each country.

M1.2: Finalisation of the metacohort list of patients: Overall, the cohort of patients have been established in all countries, totalling 25 587 patients out of an expected number of 29 000 (87.6 %). In countries with a national registry, the objective is achieved (Sweden, France, Belgium, the Netherlands) and some time exceeds the initial number of forecasted patients. On the contrary for the other countries (Germany, United Kingdom, Switzerland, Italy) where it was more time consuming to establish this list, the number of patients is more or less below the forecast; however, all these four countries improve tremendously the number of included patients. In all cases height data have been collected as well as determinants to analyze results of GH treatments on adult height and the influence of determinants as well as for mortality (WP2) and for morbidity.

M1.3: Midterm project check: Done and validated during the meeting held on 10 to 11 July 2011.
M1.4: End of WP 1, WP2 check: Done and validated during the meeting held on 6 to 7 July 2012 and some additional validation during the meeting on 11 to 12 January 2013.

M3.1: End of WP 3 check: Done and validated during the meeting held on 6 to 7 July 2012 and some additional validation during the meeting on 11 to 12 January 2013.

M4.1: Organisation of the tasks of WP4: Done and validated during the meetings held on 6 to 7 July 2012 and 11 to 12 January 2013.

M4.2: Final consortium meeting at end of the project: Done during the meeting held on 6 to 7 July 2012.

M4.2: All conclusions of all the project activities and final evaluation of the results: Done during the meeting on 11 to 12 July 2012 and 11 to 12 January 2013 - activities will however continue after this period.

M4.2: Termination of the project dissemination and planning of new extra activities after the end of the project: done during the meeting held on 11 to 12 January 2013.

M5.1: Project meeting reports every 12 months: Not done.

M5.2: Conflict of interest disclosure report: received but no formal report generated.

WP 1: Long-term efficacy of growth hormone after treatment in childhood

WP leader: APHP

The objectives of WP1 were to evaluate the following:

D1.1: Reports on adult height and its determinants;
D1.2: Reports on quality of life and their determinants.

Since collected data and methodological aspects have been detailed in the deliverables uploaded to the European Commission (EC), they will not be provided in detail here. A brief summary of the progress during this period is presented.

All patients who have started GH treatment were included, even if they have stopped treatment before completing growth. The collected data were:

1. demographic data on the patient and family, including for the child: name, given name, sex, date of birth; address of the patient's family at the time of treatment;
2. medical data relevant to the indication of GH treatment: indication (GH deficiency and its aetiology, Turner syndrome, chronic renal failure, children born short for gestational age, idiopathic short stature);
3. endocrine, genetic and radiological tests supporting the diagnosis;
4. special emphasis on diseases carrying an increased risk of secondary malignancy (such as leukaemia, CNS tumor, CNS irradiation);
5. familial and personal growth before, on and after growth hormone treatment associated treatments (i.e. sex steroids, GnRH agonists);
6. data at birth: gestational age, length and weight;
7. adult height;
8. cumulative dose of GH and GH dosing pattern.

Preexisting databases or registers supported data collection. Data have been collected from the medical records and through a questionnaire mailed to the patients. Questionnaires have been sent to all live patients. France sent questionnaires to all live patients except patients who had had a malignancy as etiology of short stature, Switzerland did not send questionnaire as well to patients who had had malignancy and chronic renal failure as etiology of short stature. These questionnaires were a precious source of information for adult height as well as for morbidity and mortality even if national registries exist.

The rate of answers is variable according to the countries rules; for instance, in Belgium, the maximum of reminder letter is
one, therefore limiting the response rate to the questionnaire. Unfortunately, no corrective actions were possible to address these issues. The rate of answers was different from a country to the other. Some of patients were abroad, or their address was wrong, some patients refused to participate to study and others did not answer. Again the rate of answers is better where national registry exists (France, Belgium, the Netherlands, Sweden).

For Italy and Germany this rate is still low probably because many addresses were wrong. United Kingdom (UK) has the lowest rate of answers but for administrative reasons this participant started later than other participants and it is probably the major reason and data collection is ongoing.

We used previously validated methodological approaches for growth analysis. The primary endpoint is height SDS gain from start of GH to adult height. The analysis is performed on the whole population and on subgroups of patients (i.e. Turner syndrome, GH deficiency, SGA).

Models have been designed to detect the effect of variables categorised as described The following questionnaires for quality of life analysis were used: SF-36, GHQ-12, socioprofessional indicators with relevant comparators available in all participating countries familial socio-professional indicators as adjustment variables. The determinants of quality of life are analysed as described with special emphasis on the role of height itself or height gain after adjustment on covariates, such as parental socio-economic class and education level. The current status of data analysis for this WP has been provided as a deliverable.

WP 2: Long term mortality and its determinants in individuals treated with growth hormone in childhood
WP leader: ICR

Since collected data and methodological aspects have been detailed in the deliverables uploaded to the EC, they will not be provided in detail here. A brief summary of the progress during this period is presented:

- determine if mortality (overall and cancer-related) is increased in a population-based sample of adult individuals treated with growth hormone in childhood;
- analyse risks of overall and cause-specific mortality in relation to GH dose, duration, age of GH treatment, time since GH treatment, and relation to background condition for which treatment was given.

This WP was scheduled to deliver results during the second half of the project. However, significant progresses were made during the first period, particularly in France, Belgium, Sweden, and the Netherland. We reproduce below the abstract of two published papers (J Clin Endocrino Metab, 97:416-425, 2012 and J Clin Endocrinol Metab 97: E213-E217, 2012); the Seventh Framework Programme (FP7) support is of course acknowledged in both. Differences in the proportion of patients belonging to different diagnostic groups and differences in the classification may explain the apparent differences between these two studies. This underlines the importance of SAGHE study.

Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: Preliminary report of the French SAGHE study
Jean-Claude Carel, Emmanuel Ecosse, Fabienne Landier, Djamila Meguellati-Hakkas, Florentia Kaguelidou, Grégoire Rey, and Joel Coste

Abstract:
All-cause and cause-specific mortality were analyzed in the French population-based register of children with idiopathic growth hormone deficiency, idiopathic short stature or born short for gestational age who started recombinant growth hormone from 1985 to 1997. Follow-up data were available for 94.7 % of the 6928 children and provided 116 403 person-years of observation. The standardised mortality ratios (the ratio of observed deaths to the number of deaths in an age-matched and sex-matched French population) was the principal outcome measure.

Results:
All-cause mortality was increased (SMR 1.33, 95 %CI 1.08 - 1.64). In univariate analysis, shorter children at start of treatment and those who had received the highest doses of growth hormone had significantly increased mortality. The use of doses higher than 50 µg/kg/d was significant in multivariate analysis adjusted on height at start of treatment (Adjusted SMR 2.94, 95 %CI 1.22 - 7.07). Mortality due to diseases of the circulatory system was increased (SMR 3.1, 95 %CI 1.41 - 5.86), bone tumors (SMR 5.0, 95 %CI 1.01 - 14.76 and subarachnoid or intracerebral hemorrhage (SMR 6.7, 95 %CI 1.80 - 17.11) was increased. Conclusion: Mortality was increased in a population of short children treated with recombinant growth hormone. High growth hormone dose, above 50 µg/kg/d, was associated with increased mortality. Specific effects were detected on death associated with bone tumours or with cerebral hemorrhage, both with plausible biological explanations. These findings question the long term safety of growth hormone.

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 three 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

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 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 years of age by the end of 2010 were included. Vital status was available for approximately 98 % of these 2543 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. Specific tasks:

- Ascertain follow-up status at a fixed end-date for each country (dead / alive / emigrated / other / loss to follow-up) and dates of exit for each exit. Multiple sources were used to obtain this information, depending on the country, and including national population registers, national health service registers, national death registers, clinical case-notes, and direct contact by mail or telephone with physicians, patients and relatives.
- Determine and gain ICD code for underlying cause of death, by obtaining information from (or copies of) death certificates in the various countries.
- Where feasible, further evaluate the cause of death using medical records and methods to obtain mortality data in the various countries. For each country, there was a need to obtain data on national mortality by age, sex and calendar year as
well as national population counts by the same parameters, to calculate 'expected' rates in the general population not treated with growth hormone. All countries have national mortality data. In Germany, 329 patients had to be excluded as date of birth is unknown. Data from Italy have not been analyzed yet because no data on end of follow-up dates are available so far. In the Netherlands, 58 deaths were assessed from the Municipal Personal Records Database. The national Death Registry did not made available individual causes of death because of strict privacy regulations. For that reason, individual causes of death had to be retrieved from medical records. The data from the Netherlands were received in January 2013. In total, 687 deaths have been identified. The current status of data analysis for this WP has been provided as a deliverable.

WP 3: Long term cancer incidence and its determinants in individuals treated with growth hormone in childhood
WP leader: KI

Since collected data and methodological aspects have been detailed in the deliverables uploaded to the EC, they will not be provided in detail here. A brief summary of the progress during this period is presented.

The objectives were to:

- to determine if cancer incidence is increased in a population based sample of adult individuals treated with growth hormone in childhood;
- to analyse the associated factors to discriminate those associated with background condition.

The results for WP3 depended again on the existence of a national morbidity and cancer registry and on the patient response rate (also depending on the validity of the mailing addresses). In several countries (France, Italy, and Germany), no national cancer registries are available and patient's response to questionnaires were important to achieve these goals. The current status of data analysis for this WP has been provided as a deliverable.

WP 5: Management

Objectives:
- To coordinate and manage the project and day-to-day progress.
- To provide a communication medium between the project partners and the EC.
- To consolidate the project planning, work control, progress reports, milestone reports, cost statements.
- To disclose and discuss potential conflicts of interests involving the project.

Project management during the period

Consortium management tasks and achievements
Pr Jean Caude Carel initiated the project and is in charge of the management of the project in collaboration with other members of the consortium. Dr Fabienne Landier is in charge of the coordination of the project and is responsible for daily communication with the SAGHE partners. She is in charge of the follow up of the study and asks regularly interim reports. She organises meeting of the consortium and teleconferences. Three in person meetings have been organised during this second period. She is in permanent relationship with Alix Pillot who is the project officer of APHP in France for financial aspects of EU projects. The website was created in July 2009 (see below).

Problems, which have occurred, and how they were solved or envisaged solutions
During this period, no major problem occurred.

Changes in the consortium, if any
None.
List of project meetings, dates and venues:
During the first period, two meetings have been held (7 to 8 December 2009 and 22 January 2011)
During the second period, three meetings have been organised:

- 10 to 11 July 2011 (Paris)
- 6 to 7 July 2012 (Paris)
- 11 to 12 January 2013 (Rome).

Project planning and status:
Report to the lay public on the major achievement 19 September 2013 during ESPE meeting (Milano).

Workshop in liaison with international organisations:
Growth hormone safety workshop, 30 to 31 January 2014 (Manchester).

Impact of possible deviations from the planned milestones and deliverables, if any:
An amendment has been accepted in May 2012 to prolong the study for 6 months. Some countries enrolled patients slower but, at the end, 87% of patients out of the initial forecast were included. For achievement of WP2 and WP3, lack of national registries for deaths and/or cancers in some countries make the tasks in these countries much more difficult and much more time consuming. No other major deviations occurred during this period. Any changes to the legal status of any of the beneficiaries, in particular non-profit public bodies, secondary and higher education establishments, research organisations and small and medium-sized enterprises (SMEs):
None.

WP 4: Translating data obtained and currently available evidence into clinical practice recommendations on growth hormone use in children for European citizens
WP leader: UTV

The main objective of WP 4 is to provide evidence-based guidelines on the use of recombinant human growth hormone (rhGH) in children at the European level, focusing on both efficacy and safety of this treatment in several medical conditions characterised by short stature. Special attention is given to:

- risk of cancer in adult subjects who underwent rhGH treatment during childhood;
- impact of growth promotion on psychosocial outcomes;
- risk / benefit balance;
- release of final document to be used as platforms for the organisation of an international consensus conference.

During the first period, we have mainly focused on safety issue after the European Medicines Agency (EMA) warning on GH long-term safety (December 2010, EMA/804468/2010). EMA started a review of the safety of somatropin-containing medicines authorised centrally or by national procedures in the EU to reassess the benefit-risk balance of these medicines. This warning followed the preliminary communication from the French Medicines Agency on preliminary SAGHE results in patients treated during childhood with somatropin-containing medicines. These preliminary SAGHE data suggested an increased risk of mortality with somatropin therapy compared to the general population. The risk appeared to be particularly increased when high doses were used.

These preliminary SAGHE results and EMA warning prompted SAGHE consortium to speed up the collection of all the available data on the safety of GH therapy, particularly focusing on mortality data.
Two scientific reports from SAGHE consortium have been published in the high impact journal, Journal of Clinical Endocrinology and Metabolism showing the long-term mortality results in France, the Netherlands, Belgium and Sweden. These preliminary data were conflicting, showing increased mortality for bone tumors or cerebral hemorrhage in the French cohort, and no increased mortality for the two conditions in the other countries. These two articles, published on the same issue of Journal of Clinical Endocrinology and Metabolism, represent the first dissemination initiative of the SAGHE consortium.

A final consortium meeting has been held in Rome, 11 to 12 January 2013. All partners have shared data on efficacy, safety, both mortality and morbidity, and quality of life. The evaluation of efficacy has been performed taking into account several factors such as: genetic predisposition (target height), anthropometry (SDS increase and cm increase in adult height, bone age delay), GH dosage (cumulative dose, dosing pattern, age at the start of treatment) and clinical conditions (GHD, Turner syndrome, SGA). The definition of prognostic factors has been derived from efficacy data. This data review process will provide evidence for a better use of rhGH, in terms of dosage, duration of therapy, therapy schedule, and appropriate indications different from GH deficiency.

Mortality rate and cancer risk has been evaluated for the different clinical conditions and for the different therapeutic regimens. Evidence for safer treatment regimen use will be derived from data of morbidity and mortality from WP2 and WP3. Both efficacy and safety data will be used to formulate guidelines and recommendations focused on the risk benefit ratio. Study data will address the issue of therapy standardisation for achieving the best results with minimal risks for patients.

All these elaborations will be presented at the following meetings:

1. At the Ninth Joint Meeting of Pediatric Endocrinology, Milan, Italy, 19 September 2013, in a 3 hours SAGHE symposium. The whole international Pediatric Endocrinology Community will attend the joint meeting in Milan, more than 5000 delegates are expected. In addition, representatives from EMA, FDA and WHO will be invited. This event will give the opportunity to share with external stakeholders the main results of the study and, at the same time, to test the external stakeholders appraisal for the study. A final round table open to the contributions of all speakers, experts in the audience, and representatives of regulatory agencies will in fact take place.

2. Another key dissemination opportunity is represented by the Growth Hormone Safety Workshop, which will be held in Manchester, UK, at the beginning of 2014. This will be a consensus workshop strongly supported by SAGHE consortium and organised and funded by the European Society for Pediatric Endocrinology, the Growth Hormone Research Society, and the American Pediatric Endocrinology Society. Representatives from EMA, FDA and WHO will be invited to attend the consensus workshop. The aim of this consensus is to provide evidence-based guidelines to be used by public health institutions, regulatory agencies, scientific societies and physicians for the use of growth hormone therapy in both childhood and adulthood.

Both the SAGHE symposium in the joint meeting and the consensus workshop involving regulatory agencies fully respect the expected deliverable (WP4, D4.2.) and milestones (WP4, M4.2). The available resources were used to fulfill the requirements for WP1, WP2 and WP3 and to organise both the final consortium meeting in Rome (M4.2) and the international symposium in Milan (WP4, D4.2, and M4.2).

Development of the project website: \text{http://saghe.aphp.fr}

This website is a public area in order to allow communication with the lay public, health care providers and patients associations to inform them and answer any question raised by the study. It is available in national languages of the participating countries. Restricted area for internal information exchange and management. The SAGHE website exists since July \text{2011}. It is accessible to every one It includes:

- general information for heath care professionals;
Website of SAGHE was updated with a communication of preliminary results on mortality of the French study and has been updated recently.

Project website: http://saghe.aphp.fr/site/spip.php/

Related information

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