Which patients with acromegaly are treated with pegvisomant? An overview of methodology and baseline data in ACROSTUDY

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Abstract

Context: Pegvisomant (Somavert, Pfizer Inc.) is the first and only available GH receptor antagonist. ACROSTUDY is an international surveillance study that offers inclusion in a web-based registry to all patients with acromegaly treated with pegvisomant; it aims at monitoring long-term safety and efficacy of this compound.

Patients and methods: This report summarizes the main baseline characteristics of this particular population of patients. In February 2009, over 300 centres in 10 countries had contributed 792 patients. A gradual increase in cumulative patient recruitment was observed since the launching of ACROSTUDY in 2004: from 116 patients in 2005, it steeply increased to 792 at the latest data freeze in February 2009. At the time of enrolment, 91.8% of patients were already treated with pegvisomant but baseline was considered at the time of pegvisomant start. IGF1 concentrations were measured at local laboratories.

Results: Of all patients, 80% were reported to have had surgery and 33% to have received radiation therapy. Of the 792 patients, 14% had received no prior medical treatment before pegvisomant start, 65.9% had received somatostatin analogues and 18.6% dopamine agonists. Interestingly, 66.7% had received only pegvisomant at study start, while it was taken in association with dopamine agonists in 5.7%, with somatostatin analogues in 23.4% and with both types of agents in 3.8%. Mean IGF1 at baseline was 522 ng/ml.

Conclusion: Analysis of the baseline features of these patients treated with pegvisomant and reported in the ACROSTUDY database underscores the severity of the disease in this subset of the population of patients with acromegaly previously unresponsive to several medical, surgical or radiation treatment approaches.

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Introduction

In the setting of clinical trials in patients with acromegaly, pegvisomant has been shown to be effective in normalising insulin-like growth factor 1 (IGF1) levels in > 90% of patients with a relatively small number of adverse events (AE) (1–4). By definition, licensing trials are designed to study drug efficacy and tolerance in strictly controlled conditions over a relatively limited period of time, while observational studies allow a longer term follow-up of larger cohorts of patients in the setting of everyday clinical use, allowing information to be gained on both safety and efficacy of the drug in a broader range of situations. As the first GH receptor antagonist and one of the few pegylated drugs, the use of Somavert (pegvisomant) requires long-term safety data collection (5, 6). ACROSTUDY is an international, multicentre, post-marketing surveillance study of pegvisomant therapy in patients with acromegaly, sponsored by Pfizer Inc. It gathers information on the ‘real-life’ use of pegvisomant, with the primary intention of accumulating long-term efficacy and safety data, especially on the outcome of tumour size during treatment. In addition, findings should clarify the clinical and metabolic consequences of GH antagonism. The present article aims at presenting the methods of data collection in the ACROSTUDY database and baseline characteristics of the 792 patients included at the
Patients and methods

Patients

At the data freeze as of February 10, 2009, summarized in the present report, 792 patients had been included. More than 300 centres in 10 countries including nine European countries and the USA have at this time contributed to the database. Most of them had thus actually already commenced pegvisomant treatment at the time of inclusion into the study. The data described as baseline refer to the time of start of pegvisomant.

ACROSTUDY

ACROSTUDY is a web-based registry that uses electronic case report forms (eCRF) to collect data, which reflect actual clinical care of patients treated by pegvisomant. The primary objective is to monitor long-term safety of pegvisomant including pituitary tumour size. The other objective is to monitor long-term efficacy of pegvisomant therapy. ACROSTUDY is open to all patients with acromegaly who are already being treated or who will start treatment with pegvisomant. The study is conducted in compliance with and consistent with the most recent version of the Declaration of Helsinki (8). In addition, all applicable local laws and regulatory requirements in the countries involved are followed. Relevant independent ethics committee in each participating country approved the study. Patients could only be enrolled after they have signed informed consent. Any patient may be discontinued from the study at any time at the discretion of the investigator or if it was the wish of the patient. ACROSTUDY is a non-interventional study, which implies that all information collected for each patient is based on the routine clinical care planned at each clinic, i.e. timing of assessments follows time points according to each clinic’s own schedule. Pegvisomant dosing and other treatment regimens are decided by each treating physician. The data are monitored for their completeness and consistency. Translations from local languages into English of free text are performed as relevant. Regulatory authorities of certain countries and/or Pfizer quality assurance staff may carry out source data checks and/or on-site inspections/audits.

The patient data are connected to a unique patient number assigned by the ACROSTUDY system. Only the clinic staff involved in the study can identify the individual behind the number. All information obtained as a result of the study is regarded as confidential until appropriate analysis and review by Pfizer and the investigator(s) are completed. The results of the study may be published or presented by the investigator(s) after the review by, and in consultation and agreement with, Pfizer, and such that confidential or proprietary information is not disclosed.

The following information available from the standard care of each patient are collected:

- Date of informed consent.
- Time of first diagnosis of acromegaly.
- Physical examination (including height, weight, blood pressure) including acromegaly related co-morbidities.
- Previous and current therapy for acromegaly; concomitant medication.
- IGF1 levels.
- Pituitary function and hormone replacement therapy.
- Pituitary imaging studies (i.e. magnetic resonance imaging (MRI), CT scan).
- Visual fields.
- Liver function tests (ALT, AST), fasting blood glucose and HbA1c (diabetic patients only).
- Symptoms (patient-assessed acromegaly symptom questionnaire, PASQ) of acromegaly during the study.
- Adverse events.

The following minimum follow-up evaluations are recommended:

- IGF1: at baseline, i.e. at commencement of pegvisomant, after 6 months of pegvisomant treatment and every 6 months thereafter. Pfizer offers a central IGF1 analysis service for participating clinics. For IGF1 analyses performed locally, in participating centres, the evaluations based on age- and sex-matched reference values are reported. The central IGF1 analysis is offered to all ACROSTUDY investigators.
- Liver function tests.
- Pituitary imaging studies: at baseline (defined as pegvisomant start), 6 and 12 months post-pegvisomant treatment start and then annually. The same imaging technique should, whenever possible, be performed throughout ACROSTUDY. All images should be kept in the hospital file. If the local neuroradiologist judges that a subsequent image shows a significant change in tumour size, whether the change is judged as clinically significant or not, all available images will be assessed by central reading. The central MRI reading is offered to all participating clinics with no additional costs. MRI has to be performed as T1-weighted spin–echo (or fast spin echo) sagittal and coronal images before and after gadolinium (T2-weighted fast spin–echo coronal images is also recommended), with 2 or 3 mm slices, preferably 2 mm. The same MR unit, observer, image parameters and amount of gadolinium should be used at follow-up.
change in pituitary tumour size was defined by a change in tumour volume of >20% in macro-adenomas or a change in the largest diameter by >3 mm in any tumour.

**Adverse events** All AE defined as any untoward medical occurrence in a patient participating in ACROSTUDY regardless of suspected causal relationship to pegvisomant are recorded on the AE page(s) of the eCRF. All serious AE should be reported within 24 h of awareness of the event by the investigator.

**Results**

**Patients enrolment**

A gradual and regular increase in cumulative patient recruitment was observed since the launch of ACROSTUDY in 2004: from 116 patients in 2005, it steeply increased to 202 in 2006, 433 in 2007, 469 in May 2008 (5) and to 792 by February 2009. As shown in Fig. 1, 10 countries had contributed to the analytical dataset at the time of present analysis: Germany, France, The Netherlands, Spain, USA, Italy, Belgium, Sweden, Denmark and Greece.

About 5% of the patients were diagnosed in the same time as enrolment in ACROSTUDY, one-third (34.7%) in the 5 years preceding enrolment in ACROSTUDY, 27.7% 5–10 years before and one-third (33.2%) at least 10 years before enrolment in ACROSTUDY. Mean time between diagnosis and enrolment was 9.5 years (median, 6.7 years). Mean time between diagnosis and pegvisomant start was 7.8 years (median, 4.5 years). Patients could be enrolled in ACROSTUDY even if they had already begun pegvisomant therapy: 65 patients (8.2%) were enrolled when they began pegvisomant or in the year following initiation of the treatment, 271 patients (34.2%) 1–3 years after initiation, 341 patients (43.1%) 3–5 years after initiation and 115 patients (14.5%) at least 5 years after initiation of pegvisomant therapy.

**Demographics**

As usually seen in patients with acromegaly, about half of patients were between 40 and 60 years of age (Fig. 2), with an even sex ratio (402 males, 390 females) in keeping with age and sex distribution observed in other acromegaly registries (9–11).

**Comorbidities/pituitary function/associated syndromes**

Most commonly reported comorbidities were hypertension (31%), diabetes mellitus (23%), arthritis and sleep apnoea (19 and 17% respectively). Other less frequent comorbidities are reported in Fig. 3. Additional pituitary dysfunctions reported at start of pegvisomant treatment included gonadotroph deficiency (23%), TSH deficiency (19%), ACTH deficiency (15%), hyperprolactinemia (7%) and diabetes insipidus (1%). Nine patients presented MEN1 (1.14% of 636 patients evaluated), eight presented McCune–Albright syndrome (1% of 638 patients evaluated) and three presented familial acromegaly.
Therapies used before pegvisomant start

Therapies reported to have been administered prior to pegvisomant treatment included surgery and/or radiotherapy, and/or medical treatments. The different combinations of treatments administered before pegvisomant start are shown in Fig. 4. Overall, ~80% of patients were reported to have had surgery, including transsphenoidal surgery in 73.3%, craniotomy in 3.8%, and 2.2% had a non-specified type of surgery. Forty-eight patients (6%) only had surgery before initiation of pegvisomant. No surgery was reported in 164 patients (20.7%); 107 had medical treatments alone (13%), 17 had both medical treatments and radiation techniques, two had radiation technique alone.

A total of 260 patients (33%) were reported to have received radiation therapy, including conventional fractionated radiotherapy in 103 (13%), stereotactic radiosurgery in 130 (16.4%) using gamma knife or linear accelerator techniques, and the type of radiotherapy used was not mentioned in 26 cases (3%). Only 5% of this cohort had received no treatment of any kind before pegvisomant start (n = 38), and overall, 14% of the patients had received no previous pharmacological treatment before pegvisomant start.

As shown in Fig. 5, most patients had received somatostatin analogue treatment by octreotide or lanreotide. About 20% patients had previously been treated by dopamine agonist drugs, alone or in combination. Pegvisomant replaced somatostatin agonists and/or dopamine agonists mainly because of uncontrolled IGF1 level (> 50% cases), or bad tolerance to previous medical treatments (10–15% cases). Interestingly, 66.7% of patients received only pegvisomant at the time of enrolment in ACROSTUDY, while it was taken in association with dopamine agonists in 5.7%, with somatostatin analogues in 23.4% and with both types of drugs in 3.8%. Information on the patients on combination therapy was however not further detailed for the present analysis and will have to be studied specifically.

Initial IGF1 levels

Pre-pegvisomant IGF1 concentrations were reported in 509 (64%) patients. Mean IGF1 levels at baseline, i.e. at pegvisomant start was 522 ng/ml with broad variations according to centres or countries largely attributable to the inter-assay variability between the different assay methods used. As expected, as shown in Fig. 6, age-related variations were mostly marked at extremes: 692 ng/ml in patients below 30 years of age versus 417 ng/ml in patients over 60, while IGF1 values varied between 495 and 516 ng/ml in intermediate 10-year age intervals. Mean IGF1 concentrations were similar in men and women (520 vs 512 ng/ml). As expected in the majority of patients, IGF1 concentrations were evaluated as above age- and gender-reference values. Surprisingly, in 74 patients, the values were assessed as normal, and in two patients, the values were below normal ranges.

Figure 4 Therapy before pegvisomant start in a total of 792 patients in ACROSTUDY. The numbers of patients in each category of treatment combination (and percentage of the total number of patients in parentheses) are indicated in the circles.

Figure 5 Pharmacological treatment at any time before pegvisomant treatment. Dopamine agonist therapy is depicted in black bars, somatostatin analogue therapy in grey bars. Percentages (indicated above bars) of patients who have received each type of treatment. Total exceeds 100% as many patients have received several types of pharmacological treatments.

Figure 6 Age-related IGF1 (ng/ml) at enrolment. Number of patients is indicated above bars. Mean IGF1 values are indicated inside bars for each age group.
Discussion

Treatment of acromegaly involves several different modalities, including transsphenoidal surgery (12), conventional radiotherapy or stereotactic radiosurgery (13), and obviously medical treatments (14, 15). In current clinical practice, somatostatin analogues usually remain the first-line medical treatment. Pegvisomant is the first and only available GH receptor antagonist. The first patients with acromegaly received their first doses of treatment with pegvisomant, which at that time was referred to as B2036-PEG 12 years ago. Since March 2003, following approval by the USA Food and Drug Administration, the drug has been available on the market under the brand name Somavert. As a consequence of relatively short history, pegvisomant still requires long-term tolerance and efficacy data (2, 3). ACROSTUDY, an international, multicentre, post-marketing surveillance study of pegvisomant therapy in patients with acromegaly, sponsored by Pfizer Inc., aims at providing evidence on both safety and efficacy data (5, 6). In the present manuscript, we presented – with a detailed description of the ACROSTUDY protocol – an analysis of the baseline characteristics of 792 patients included in ACROSTUDY. A steep increase in cumulative patient enrolment was observed since the start of the study 5 years ago, allowing analysis of a substantial number of patients treated in various countries all over the world with the aim to provide participating clinicians with useful information on this drug. Previous analyses of the German pegvisomant observational study (16, 17) have already given useful insights into the ‘real-life’ use of pegvisomant and assisted physicians with issues such as optimising dose titration (6). Several countries have organized national registries of patients with acromegaly, which contribute to gain insights on the actual conditions of diagnosis and treatment of this rare disease (10, 11, 18). The French Acromegaly Registry represents one such register that could be used to compare the profile of a general population of patients with acromegaly to the subset of patients treated with pegvisomant and included into ACROSTUDY.

Demographic characteristics of ACROSTUDY population did not show evident difference compared with the classical characteristics of patients with acromegaly in terms of age and sex ratio (French Acromegaly Registry, unpublished data). ACROSTUDY population also did not differ in terms of comorbidities presumably in part due to concomitant therapies of each particular complication, nor in terms of associated pituitary hormone deficiencies. Despite the fact that pegvisomant is currently marketed as second or third line therapy, no previous treatment was reported in 5% of patients in the ACROSTUDY. Even if this latter point could be explained, at least in part, by underreporting, it shows that pegvisomant is now considered by some physicians as a first-line treatment. The other indications remain resistance to somatostatin analogues (defined by high IGF1 levels despite maximal dose of somatostatin analogues) or bad tolerance to other medical treatments. Another profile of patients, with likely more severe GH hypersecretion, might benefit from the association of somatostatin analogues with pegvisomant (19, 20). With about 25% patients receiving combination therapy in the ACROSTUDY population, such treatment pattern seems to be frequently used by physicians. For this specific report, we did not try to evaluate the reasons why combination therapy had been used; it however makes sense that patients inadequately controlled by somatostatin analogues and by pegvisomant alone, or presenting with a relatively large tumour size (to avoid a theoretical risk of increase in tumour size with pegvisomant (21)) might have been prescribed both treatments. Another report (22) also suggested potential positive effects of the association on quality of life compared with somatostatin analogues alone, but these reports are probably too recent to yet induce modified prescriptions.

Interestingly, though rarely reported in the literature, about 6% of the patients were treated by the association of dopamine agonists with pegvisomant; to our knowledge, this association has never been previously evaluated as a treatment of acromegaly. This way of treatment might be used in case of intolerance to somatostatin analogues and partial inefficacy of pegvisomant, or in case of prolactin–GH-secreting adenoma.

Do the patients treated by pegvisomant suffer from more severe GH hypersecretion? One of the best criteria to determine the level of severity of acromegaly in patients treated by pegvisomant would have been IGF1 levels before initiation of the treatment. Once again, comparison of mean IGF1 level in ACROSTUDY patients and in the French Acromegaly Registry does not show any evident difference. Obviously, the fact that the majority of these patients had previously been treated by a large number of therapeutic modalities (only 38 out of the 792 patients had had no treatment before pegvisomant, while most patients had at least surgery and medical treatment, and 30% additional radiation treatment) shows that, despite the fact that pegvisomant was occasionally proposed in some cases as a first-line treatment, it remains mainly prescribed as a complementary treatment in patients with severe acromegaly (as currently marketed).

As previously explained, limitations of ACROSTUDY in defining the profile of the population treated to date by pegvisomant mainly concern three points: the first is the fact that in the majority of patients pegvisomant therapy was initiated before enrolment into ACROSTUDY, which may partly explain the relatively high proportion of patients with missing data on pre-pegvisomant IGF1 concentrations. It should be remembered that baseline visit was set at pegvisomant start. Another important methodological point worth underlining is that, despite possibility of central analysis...
of IGF1 offered to all ACROSTUDY investigators, very often reported IGF1 concentrations were measured at local laboratories. Although evaluations based on age- and sex-matched references from each centre are reported, this should obviously be kept in mind when interpreting IGF1 values that may differ from centre to centre because of analytical reasons. The last point is a bias of most observational studies: there is indeed always a risk of underreporting effects or poor knowledge of previous history of the patient, thus leading to possibly biased interpretations. Despite all these limitations, ACROSTUDY remains a very important database providing additional information on pegvisomant use, its efficacy and safety profile (reported by Trainer et al. current issue).

To conclude, ACROSTUDY is now underway at > 300 sites in 10 countries. This cohort of patients treated with pegvisomant and reported in the ACROSTUDY database might represent a subset of the population of patients with severe acromegaly, as these patients previously proved unresponsive to several medical, surgical or radiation treatment approaches. Overall, ACROSTUDY will provide a better understanding of the characteristics of patients treated with pegvisomant in clinical practice.

Declaration of interest
T Brue is a consultant for Ipsen, Novartis and Pfizer. F Lundgren and M Kolowska-Häggström are employees of Pfizer Health AB. P Petrosians received compensation for his collaboration to the French Acromegaly Registry, which is supported by an unrestricted educational grant from the French branches of Ipsen, Novartis and Pfizer. ACROSTUDY™ is sponsored by Pfizer Inc. This paper forms part of a European Journal of Endocrinology supplement, supported by Pfizer Inc.

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