Long-Term Safety of Pegvisomant in Patients with Acromegaly: Comprehensive Review of 1288 Subjects in ACROSTUDY

A. J. van der Lely, Beverly M. K. Biller, Thierry Brue, Michael Buchfelder, Ezio Ghigo, Roy Gomez, Judith Hey-Hadavi, Frida Lundgren, Natasa Rajicic, Christian J. Strasburger, Susan M. Webb, and Maria Kołtowska-Häggström

Department of Medicine (A.J.v.d.L.), Erasmus University Medical Center, 3000 CA Rotterdam, The Netherlands; Harvard Medical School (B.M.K.B.), Massachusetts General Hospital, Boston, Massachusetts 02114; Department of Endocrinology (T.B.), Centre de Référence des Maladies Rares d'Origine Hypophysaire, Hôpital de la Timone, Assistance Publique-Hôpitaux de Marseille and Faculté de Médecine de Marseille, Aix-Marseille Université, 13331 Marseille, France; Department of Neurosurgery (M.B.), Neurochirurgische Klinik, 91054 Erlangen, Germany; Department of Endocrinology (E.G.), University of Turin, 10126 Turin, Italy; European Medical Affairs (R.G.), Pfizer, 1050 Brussels, Belgium; Medicines Development Group (J.H.-H., N.R.), Clinical Affairs, Pfizer Inc., New York, New York 10017; ACROSTUDY (F.L., M.K.-H.), Pfizer Health AB, 191 90 Sollentuna, Sweden; Division of Clinical Endocrinology (C.J.S.), Department of Medicine, Campus Charité-Mitte, 10117 Berlin, Germany; and Departments of Endocrinology and Medicine (S.M.W.), Hospital Sant Pau, IIB-Sant Pau, Centro de Investigación Biomédica en Red de Enfermedades Raras Unit 747, Instituto de Salud Carlos III; Universitat Autònoma de Barcelona, 08025 Barcelona, Spain

Context: Pegvisomant is a GH receptor antagonist. The ACROSTUDY is a global safety surveillance study of long-term treatment of acromegaly with pegvisomant.

Objective: The objective of the study was to monitor long-term safety and treatment outcomes.

Design: ACROSTUDY is open to all patients with acromegaly who are treated with pegvisomant. We report an interim analysis of data captured from 1288 subjects enrolled before a database freeze of December 31, 2009.

Setting: This was a global noninterventional surveillance study.

Main Outcome Measure(s): Long-term monitoring of safety, including central magnetic resonance imaging (MRI) reading and treatment outcomes, was measured.

Results: Subjects (n = 1288) were treated with pegvisomant for a mean of 3.7 yr and followed up in ACROSTUDY for a mean of 2.1 yr. A total of 1147 adverse events (AE) were recorded in 477 subjects (37%), among which 192 AE in 124 subjects (9.6%) were considered to be related to pegvisomant. Serious AE were recorded in 159 subjects (12.3%), whereas pegvisomant-related Serious AE were recorded in 26 subjects (2%). No deaths (15 subjects; 1.2%) were attributed to pegvisomant use. The incidence of increase in pituitary tumor size in the subset with confirmed MRI increases on central reading represented 3.2% of the overall cohort with at least two available MRI (n = 936). Injection-site reactions were reported in 28 cases (2.2%). In 30 patients (2.5%), an elevated aspartate aminotransferase or alanine aminotransferase of more than 3 times the upper level of normality was reported. There were no reports of liver failure. After 5 yr of pegvisomant treatment, 63.2% of subjects had normal IGF-I levels at a mean dose of 18 mg/d.

Conclusions: Data entered and evaluated in ACROSTUDY indicate that pegvisomant is an effective and safe medical treatment in patients with acromegaly. The reported low incidence of pituitary tumor size increase, liver enzyme elevations, and lipodystrophy at the injection site are reassuring. **(*J Clin Endocrinol Metab* 97: 1589–1597, 2012)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2011-2508 Received September 8, 2011. Accepted January 25, 2012.
First Published Online February 22, 2012

Abbreviations: AE, Adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver enzyme; MRI, magnetic resonance imaging; SAE, serious AE; ULN, upper level of normal.

Pegvisomant is a GH receptor antagonist, which is used in the treatment of acromegaly. The first reports on safety and efficacy of pegvisomant were published in the early years of this century (1, 2). Pegvisomant was approved in the United States in 2003 followed by the approval in Europe in 2004.

Established in 2004, ACROSTUDY is a global noninterventional safety surveillance study of long-term treatment with pegvisomant. The objectives are to monitor the long-term safety and treatment outcomes of pegvisomant in patients with acromegaly. ACROSTUDY is open to all patients with acromegaly who are treated, or planned to be treated, with pegvisomant in routine clinical practice and contains a growing volume of data on patients with this rare disease. An important part of the current data set has been provided by the German Pegvisomant Observational Study, initiated in January 2004 immediately after pegvisomant received market authorization in Germany. The German Pegvisomant Observational Study added 254 additional patients to the ACROSTUDY database, which at the time included 310 patients (3).

Phase IV noninterventional studies like ACROSTUDY, also known as surveillance trials, are an accepted method of providing medical information complementary to placebo-controlled, randomized clinical trials (4). Such studies capture information about clinical characteristics and patient management in large cohorts followed up in routine clinical settings (5). They are particularly well suited for collecting infrequent adverse events and atypical treatment reactions in rare disorders like acromegaly (5).

An interim analysis of data in ACROSTUDY was planned for after approximately 1000 subjects were enrolled, and the study had been conducted for at least 5 yr. Herein is the report of this analysis, presenting the data from the ongoing ACROSTUDY, with a special focus on liver tests and pituitary tumor size because several previous raised the possibility that alterations in these parameters were related to pegvisomant (6–9).

Materials and Methods

ACROSTUDY is an ongoing open-label, global, noninterventional, postmarketing safety surveillance study open to patients with acromegaly who are treated with (or about to begin) pegvisomant, intended to monitor long-term safety and outcome in routine clinical practice. This report presents the interim analysis of data in the ongoing ACROSTUDY, from 1288 subjects who were enrolled as of December 31, 2009.

Data regarding physical examination, medical history, and laboratory evaluations were captured from routine visits using information available in the clinical records; no additional diagnostic or monitoring procedures were conducted as part of the study. All parameters were collected by the local investigators on electronic case report forms using a web-based tool. A unique patient identification number was assigned to each patient by the ACROSTUDY data-capturing system, which allowed only the team at the study site to identify the individual patient associated with the number.

The following baseline evaluations were requested: pituitary imaging studies, liver tests, and IGF-I levels. Baseline was defined as the start of pegvisomant treatment, regardless of when ACROSTUDY enrollment occurred. Because this was a noninterventional study, the treatment dose and frequency, as well as the timing of follow-up visits, pituitary imaging and laboratory evaluations were at the discretion of each treating physician/investigator who was aware of local pegvisomant prescribing information. The protocol recommended the following minimum follow-up evaluations: pituitary imaging at 6 and 12 months after pegvisomant treatment start, and then annually, and liver tests and IGF-I levels every 6 months. Central IGF-I analysis was offered to participating clinics but was infrequently used. Therefore, only locally measured IGF-I data are reported in relation to local reference values. Both historical and prospective data were collected during the study.

Main criteria for inclusion and exclusion

The study included subjects with acromegaly who were already being treated with pegvisomant as well as those who were about to start. Pediatric practice differed by region; because safety and efficacy of pegvisomant in children had not been established, the European Medicines Agency requested that physicians using pegvisomant in pediatric subjects enroll them in ACROSTUDY. In Italy and the United States, however, only subjects over the age of 18 yr were eligible for enrollment.

The most important exclusion criteria were patients without a diagnosis of acromegaly, participating in any clinical trial of an investigational drug for acromegaly, requiring surgical decompression of tumor (such as in contact with the optic chiasm) or who should have nonmedical therapy because of visual field loss, cranial nerve palsies, or intracranial hypertension.

The ACROSTUDY data reported here were collected in compliance with, and consistent with, the most recent version of the Declaration of Helsinki. In addition, all applicable local laws and regulatory requirements in the countries involved were adhered to. Local ethical approval was obtained for all participating centers, and all patients provided written informed consent before any data were captured.

Central magnetic resonance imaging (MRI) reading

The protocol recommended that the local MRI procedure use the same imaging technique and equipment whenever possible throughout ACROSTUDY. The MRI protocol recommended T1-weighted spin-echo (or fast spin echo) sagittal and coronal images before and after gadolinium, and T2-weighted fast spin-echo coronal images. If the local radiologist reported a significant change in pituitary tumor size, irrespective of whether the change was considered clinically important, all available images for that patient were to be sent for central assessment. The central MRI readers were blinded to all clinical data except for exposure to pegvisomant. From all available images, those depicting the tumors in comparable sections were selected. Paper prints and semitransparent films were digitalized and corrected for gray scale and magnification. In most patients, sections depicting the infundibulum were used. A manual segmentation of the carotid

arteries, sellar contents, normal pituitary, and adenoma was performed and volume changes assessed. A significant change in pituitary tumor size by central reading was defined as a change in the largest diameter by more than 3 mm. In macroadenomas, an additional criterion of greater than 20% increase or decrease in tumor volume was used.

Other safety evaluations

Safety was also evaluated by collection of adverse events (AE) and laboratory data as reported by investigators. An AE was considered any untoward medical occurrence reported in a patient participating in ACROSTUDY; the event did not necessarily have a causal relationship with pegvisomant. Serious AE (SAE) were defined as AE that were fatal or life threatening, required hospitalization, or prolongation of existing hospitalization resulted in *in utero* exposure or permanent or serious disability/incapacity. AE were coded according to the *Medical Dictionary for Regulatory Activities*, version 12.1; SAE frequencies were displayed according to the *Medical Dictionary for Regulatory Activities* version 13.1 (http://www.meddramsso.com/). For subjects on pegvisomant before entering ACROSTUDY, AE data before study entry were considered to be part of the medical history and reported in the database if deemed relevant. Additionally, comorbidities, particularly diabetes, hypertension, cardiovascular and cerebrovascular disease, respiratory tract disorders, osteoarthritis, benign and malignant tumors, sleep apnea, and hepatic diseases diagnosed before pegvisomant start were to be reported. These data, recorded by the physician/investigator as comorbidities at study entry, are presented separately from the AE that occurred during ACROSTUDY. Any aggravation of a preexisting condition during ACROSTUDY was to be reported as an AE. Discontinuations due to nonserious AE and severity of AE were not captured.

Statistical methods

For this noninterventional, observational safety study, there were no prespecified statistical hypotheses to be tested. All analyses were planned as descriptive summaries. The full analysis set consisted of all subjects who entered ACROSTUDY and received at least one dose of pegvisomant. For each subject, baseline was defined as the start of pegvisomant treatment, regardless of their date of enrollment into ACROSTUDY. The protocol stipulated that all available data (historical and prospective) after the pegvisomant start were to be summarized.

Results

Overall, 1288 subjects were enrolled from 12 countries in ACROSTUDY by December 2009 as follows: Germany (n = 399), France (n = 198), Italy (n = 185), Spain (n = 178), The Netherlands (n = 95), the United States (n = 81), the United Kingdom (n = 39), Greece (n = 29), Denmark (n = 28), Belgium (n = 24), Sweden (n = 23), and Slovakia (n = 9).

Patient characteristics

Most subjects (93.4% of the 1288) were Caucasian and 51% were male. The mean age at diagnosis of acromegaly was 42.1 yr (range 1.7–83.7 yr). Acromegaly was diagnosed at younger than 18 yr in 33 subjects and 25 subjects were over 70 yr old at diagnosis. At ACROSTUDY start, there were five subjects between 0 and 18 yr and 127 subjects over 70 yr of age. The mean age at pegvisomant start was 49.8 yr (range 3.9–85.6 yr). Mean ± SD body mass index (kilograms per square meter) was 30 ± 4.8 for men and 29 ± 6.2 for women.

The majority of the 1288 subjects (n = 954) had undergone pituitary surgery, 54 of whom had surgery alone. A total of 362 subjects had received radiotherapy; in one subject this was the only treatment. Twenty-six subjects had been treated with both surgery and radiotherapy, without prior medical therapy. A total of 1131 subjects had already received other medical treatment before the start of pegvisomant. Of these subjects, 560 had also undergone surgery, whereas another 314 subjects had received all three interventions (surgery, radiotherapy, and medication). Only 21 subjects had received the combination of radiotherapy and medical therapy without surgery.

Pegvisomant was used before enrollment in ACROSTUDY in 1046 subjects (81.2%). The median time from the start of pegvisomant to enrollment in ACROSTUDY was 489 d (~1.3 yr). Overall, subjects had undergone a mean of 3.7 yr (range 0–12.5 yr) of the pegvisomant treatment.

In 1023 of the 1288 subjects (79.4%), at least one comorbidity was reported before pegvisomant start. The most common were hypertension (50.5%), diabetes mellitus (33.2%), osteoarthritis (24.1%), sleep apnea (21.8%), and thyroid tumors (either benign or malignant; 21%). In 413 subjects, new comorbidities were reported after pegvisomant start. New comorbidities before and after pegvisomant start were similar.

Safety events reported in the study

Adverse events

Subjects were followed up in ACROSTUDY for a mean of 2.1 yr (range 0–5.5 yr). A total of 1147 AE were recorded in 477 subjects (37% of 1288 subjects), among which 192 in 124 subjects (9.6%) were considered by the clinician/investigator as related to pegvisomant.

More than half of the reported AE were infrequent and considered unrelated to pegvisomant. They included events such as dry eyes, tooth loss, hordeolum, pyrexia, and nail disorder. The most common remaining AE were in the areas of hematology, cardiology, endocrinology and metabolism, and oncology. The most frequently reported all-causality AE (so including those linked to the use of pegvisomant) were recurrent pituitary tumor (29 subjects), headache (26 subjects), increased transaminases (19 subjects), hypertension (18 subjects), arthralgia (17 subjects), colonic polyp (15 sub-

TABLE 1. AE and SAE in ACROSTUDY

	All causalities	Treatment related
Patients evaluable for AE	1288	
Number of AE	1147	192
Patients with AE	477 (37.0%)	124 (9.6%)
Patients with SAE	159 (12.3%)	26 (2%)
Permanently discontinued due to SAE	22 (1.7%)	4 (0.3%)
Death	15 (1.1%)	0
Dose reduction due to SAE	24 (1.9%)	10 (0.8%)

The table shows both the AE and SAE that were related by the investigators to the use of pegvisomant as well as the all causalities AE and SAE.

jects), increased hepatic enzyme (13 subjects), and 12 subjects each with increased alanine aminotransferase (ALT), increased glycated hemoglobin, and diabetes.

AE considered to be related to pegvisomant were changes in tumor size and liver enzymes as well as injection site events.

Serious adverse events

SAE are separate reports from the AE. SAE were recorded in 159 of 1288 subjects (12.3%), whereas SAE reported as pegvisomant related were recorded in 26 subjects (2%). Dose reduction due to an SAE was reported in 24 subjects (1.9%); in 10 of those 24 subjects, the SAE was considered related to pegvisomant (Table 1).

During ACROSTUDY, the most frequently reported SAE were recurrent pituitary tumor (19 subjects), pituitary tumor removal (eight subjects), increased hepatic enzymes (12 subjects), and pneumonia (four subjects). Other SAE reported for laboratory test abnormalities included one subject each with increased levels of creatinine, γ-glutamyltransferase, and IGF-I. All SAE of increased hepatic enzymes, transaminases, and γ-glutamyltransferases were considered by the investigators to be related to pegvisomant. Two SAE relating to pregnancies were reported; one was an SAE of elective abortion and the other was a male subject whose partner was pregnant (fetal exposure *in utero*). Twenty-six subjects had SAE that were reported to be treatment related, and 22 subjects discontinued treatment due to SAE (see Table 2).

Mortality in ACROSTUDY

Overall, 15 deaths (1.2% of 1288 subjects) were reported in the study. None was considered by the investigator to be related to the use of pegvisomant. The most frequent causes of death were heart failure (n = 4) and cancer related (n = 4).

TABLE 2. Discontinuation due to SAE in 22 subjects in ACROSTUDY, including the 15 deaths

SAE	n	Number of deaths
Pituitary tumor size ↑	6	0
Hepatic enzymes ↑	2	0
Metastatic cancer	4	4
Unexpected sudden death	1	1
Circulatory collaps	1	1
Pancreatitis	1	1
Cardiac arrest	1	1
Cerebrovascular accident	1	1
Cardiac failure	4	4
Pneumonia	1	1
Subarachnoid hemorrhage	1	1
Total	22	15

Pituitary tumor size

Of the 1213 subjects with pituitary imaging, 936 subjects had one or more pituitary image reported after pegvisomant start (scans taken ≥30 d after pegvisomant start) (Fig. 1).

The local radiologist reported no change in the tumor relative to the last examination or to pegvisomant start in 738 subjects (78.8% of 936 subjects). In 198 subjects (21.2%), a change in tumor size was reported. Of the 198 subjects with a change reported, a decrease in tumor size was described more often (12.6% of 936 subjects) than an increase (7.2% of 936 subjects). Both an increase and a decrease were reported in 1.4% of 936 subjects. Central MRI re-reading was performed on individual series of scans from 128 subjects (121 subjects with change and seven subjects without change reported on local MRI reading) by the time of this analysis.

Overall, among the 128 central MRI re-readings, 23 patients had an increase in tumor size, 38 patients showed a decrease in tumor size, seven patients had increase and a decrease in tumor size over several scans, 41 patients showed no change, and 19 patients had insufficient data (Table 3). In 13 of the 30 cases in which we measured an increase in tumor size, the increase in size was considered to be of clinical significance. Tumor increase was documented by central MRI reading in 14 of the 45 patients (31.1%) with a locally reported increase, in just four of 11 patients with a reported increase and a decrease and in two patients considered locally to have a decrease in tumor size. Tumor regression was reported after central MRI reading in 27 of the 64 patients (42.1%) with a locally reported decrease. Finally, 21 of those 64 patients had stable tumors and two had an increase in size on central review. Taken together, the subset with confirmed MRI increases or increases/decreases based on central reading represented 3.2% of the overall cohort of 936 subjects with at least two available MRI.

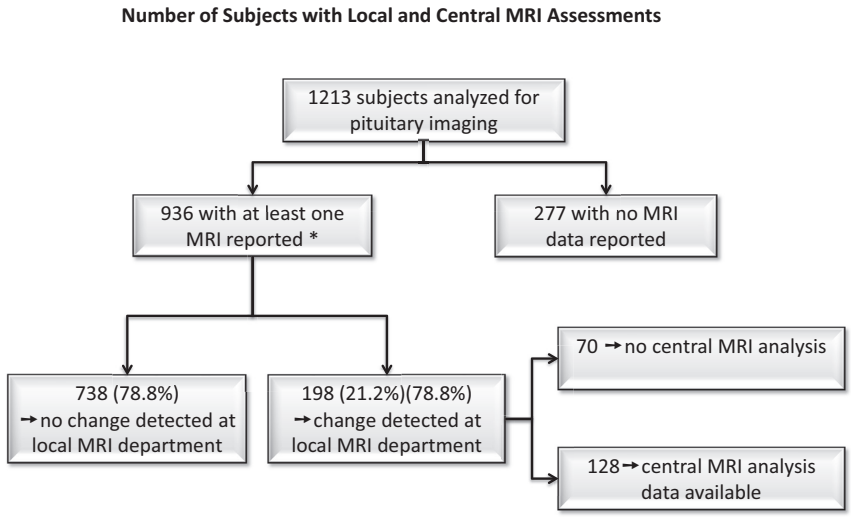

FIG. 1. Number of subjects with local and central MRI assessments. *, One or more pituitary images reported 30 d or longer after the start of pegvisomant.

Injection-site reactions

The most frequently reported pegvisomant-related AE in ACROSTUDY were 28 cases (2.2% of 1288 subjects) of injection-site reactions. These were categorized as lipodystrophy or lipohypertrophy (n = 16), pruritus (n = 9), injection-site dystrophy (n = 2), and injection-site hemorrhage (n = 1).

Liver tests

ALT and aspartate aminotransferase (AST) were normal at baseline in 536 and 556 subjects of the 1288 subjects, respectively, whereas in 50 and 27 subjects, ALT and AST were already abnormal at baseline.

In 1178 of the 1288 subjects (91.5%), at least one liver enzyme test (ALT or AST) after pegvisomant start was available. Of these 1178 patients, 30 (2.5%) had an elevated AST or ALT reported greater than 3 times the upper level of normal (ULN), regardless of baseline. The changes in AST or ALT were recorded after a median of 152 d (range 42–1144 d). More detailed information on these 30 subjects is provided in Table 4. Somatostatin analogs were also being administered when the rise in AST or ALT was detected in 19 of the 30 subjects (63.3%). The combined use of both pegvisomant and somatostatin analogs reported by the treating physicians was around 25% (of 1163 subjects) 1 yr after enrollment and around 27% (of 349) after 5 yr. For 23 subjects with follow-up laboratory tests available, AST and ALT reversed to baseline levels after decrease or discontinuation of pegvisomant in some but not all (see Table 4).

There were no reports of liver failure.

The most frequently reported liver-related AE were steatosis (n = 8), hepatic cyst (n = 7), cholelithiasis (n = 7), Gilbert's syndrome (n = 4), hemangioma (n = 4), hepatitis A (n = 2), hepatitis C (n = 2), hypotrophic liver lobe (n = 1), cancer (considered unrelated to pegvisomant) (n = 1), chronic fibrotic cholangitis (n = 1), and hepatitis B (n = 1).

Treatment outcomes of pegvisomant

Dose frequencies and dose of pegvisomant in relation to efficacy

The vast majority of patients used pegvisomant as daily injections (88%), whereas 12% of patients took injections less frequently. After respectively 1 and 5 yr of treatment, 31.5 and 36.6% of subjects used pegvisomant in combination with another medical treatment modality for acromegaly (mainly somatostatin analogs).

After 5 yr of pegvisomant treatment, 63.2% of subjects had normal IGF-I levels, whereas in 34%, the IGF-I levels remained elevated. The proportion of patients with normal IGF-I levels remained stable over time. The mean dosages after 5 yr, expressed as milligrams per day, were 18 for the controlled group and 20 mg for the uncontrolled group (Fig. 2).

Discussion

The ACROSTUDY database provides an opportunity to assess long-term safety of pegvisomant in the treatment of

TABLE 3. Pituitary tumor imaging data during pegvisomant therapy: central and local reading data of MRI

Local MRI (n = 936)		Central MRI (n = 128)					
		Increase	Decrease	Increase + Decrease	No change	Insufficient data	Not done
	n	23	38	7	41	19	809
Increase only	67	14	6	4	16	5	22
Decrease only	118	2	27	2	21	12	54
Increase + decrease	13	4	3	1	2	1	2
No change	738[a]	2	2	0	2	1	731
Missing	1	1	0	0	0	0	0

[a] Central MRI was not required when locally there was no change in tumor size observed.

TABLE 4. Descriptive analyses of the 30 subjects who showed changes in ALT or AST above 3 × ULN that were observed and reported as an AE or SAE

No.	Sex	Age (yr)	Somatostatin medication	Pegvisomant dose	New pegvisomant dose	Reversibility	Replacement medication	Other medication
1	M	54	120 mg LAN/month	60 mg weekly	Stopped	Unknown	T_4, HC, Test	
2	M	60	60 mg LAN/month	20 mg daily	Stopped	Reversible	T_4	Sulfazalazine
3	F	63		10 mg daily	Unchanged	Unknown		
4	F	58		15 mg daily	Dose delayed	Reversible		Bromazepam, meprinizine
5	F	46	60 mg LAR/month	20 mg daily	Unknown	Unknown		>20 drugs
6	M	35	30 mg LAR/month	20 mg daily	Unknown	Reversible	T_4, HC	Lansoprazol, trandolapril
7	M	57	30 mg LAR/month	30 mg daily	Unchanged	Reversible	T_4, Test	Simvastatin, omeprazol, nebivolol
8	F	68		40 mg daily	Unchanged	Reversible	T_4, HC	Amlodipine, valsartan, cabergoline
9	M	47		25 mg daily	Unchanged	Reversible		>20 drugs
10	F	44	30 mg LAR/month	15 mg daily	10 mg daily	Reversible	T_4, HC	
11	M	48		15 mg daily	Unchanged	Reversible	T_4, HC	Cetirizin
12	F	59	30 mg LAR/month	10 mg daily	Dose delayed	Reversible		Atorvastatin
13	F	61		10 mg daily	Dose delayed	Reversible	T_4, HC	Atorvastatin, esomeprazole, nebivolol
14	F	59	30 mg LAR/month	10 mg daily	Unchanged	Reversible		>5 drugs
15	F	42		10 mg daily	Unchanged	Reversible		
16	F	70	Octreotide sc	10 mg daily	Dose delayed	Reversible		Clonazepam, omeprazol, zolmitriptan
17	F	51		25 mg daily	Unchanged	Reversible	T_4, HC	Insulin, ramipril, propranolol
18	F	36		20 mg daily	Unchanged	Reversible	T_4, HC, E2	Omeprazol, bromocriptin
19	F	50	30 mg LAR/month	20 mg daily	Dose delayed	Reversible		Atenolol
20	M	72	30 mg LAR/month	60 mg/wk	Stopped	Reversible		Insulin + >5 drugs
21	M	39	60 mg LAR/month	30 mg daily	Unchanged	Unknown	Test	
22	F	42	20 mg LAR/month	60 mg/wk	Unchanged	Reversible		
23	M	60	30 mg LAR/month	20 mg daily	Unchanged	Reversible	Test	
24	M	47	10 mg LAR/month	10 mg daily	Unchanged	Reversible		Calcitrol, telmisartan
25	M	64	20 mg LAR/month	10 mg daily	Unchanged	Reversible		>5 drugs
26	M	46	20 mg LAR/month	10 mg daily	2 × 20 mg/wk	Reversible	T_4, Test	Enalapril
27	M	42	30 mg LAR/month	10 mg daily	Stopped	Unknown		
28	F	60	60 mg LAR month	20 mg daily	Dose delayed	Reversible	T_4	Lisinopril, metoprolol
29	F	4		30 mg/wk	20 mg/wk	Unknown		
30	F	36		15 mg daily	Dose delayed	Unknown	T_4	

F, Female; M, male; LAR, sandostatin long-acting release; LAN, lanreotide autogel; HC, hydrocortisone; E2, estradiol; Test, testosterone.

acromegaly. Based on earlier pegvisomant trials, the main safety focus was on the potential risk of increased pituitary tumor size. In addition, liver enzyme (LFT) elevations and effects of pegvisomant at the injection site were also assessed, as they have been previously reported side effects (2, 9–16).

Noteworthy is that most subjects were enrolled in Europe, where pegvisomant is registered for patients in whom every other therapeutic intervention failed to control their acromegaly. This implies that a selection bias is present in ACROSTUDY that overincludes patients with the worst acromegaly disease activity and the most comorbidities.

One of the important findings presented here was the very low percentage of patients with a clinically relevant increase in tumor size. As shown in Fig. 1 and Table 3, of the 45 subjects with suspected pituitary tumor growth, only 14 had an increase confirmed after reevaluation of the series of scans by central reading. Moreover, of the additional 64 subjects with data assessable on central reading, another 14 subjects showed an increase in tumor size, despite no increase reported by the investigator. Thus, central reading showed that as of December 2009, the subset with confirmed MRI increases or increases/decreases based on central reading represented 3.2% of the overall cohort with at least two available MRI. These findings indicate that tumor growth is uncommon during pegvisomant treatment and that central assessment of sequential pituitary images yields different results compared with local center readings. Comparison of images from multiple investigations is technically difficult and extremely labor intensive. Digitalization is usually not performed in clinical practice. The gantries, sequences for image acquisition, and resolution often differed widely between scans and creating a high potential for interpretation errors. Only careful analysis of an entire series of images as described above provides a more precise estimation of tumor volume changes. The findings suggest that increases in tumor size reported locally may be an overestimation. The rate of tumor size increase may be closer to earlier clinical trials (*i.e.* ~3%).

Importantly, according to the protocol, any change reported by the local radiologist was to trigger systematic central review of all images in that patient. Limitations of the study are that not all of the MRI in such subjects were actually sent for central reading, and no scans considered stable on local reading were sent for central review.

Of 1178 patients with at least one liver test reported, 30 (2.5%) had an AST or ALT above 3 × ULN. This is a reassuring incidence compared with other reports on long-term safety and efficacy of pegvisomant (10, 15, 17). Interestingly, Table 4 shows that the majority of subjects

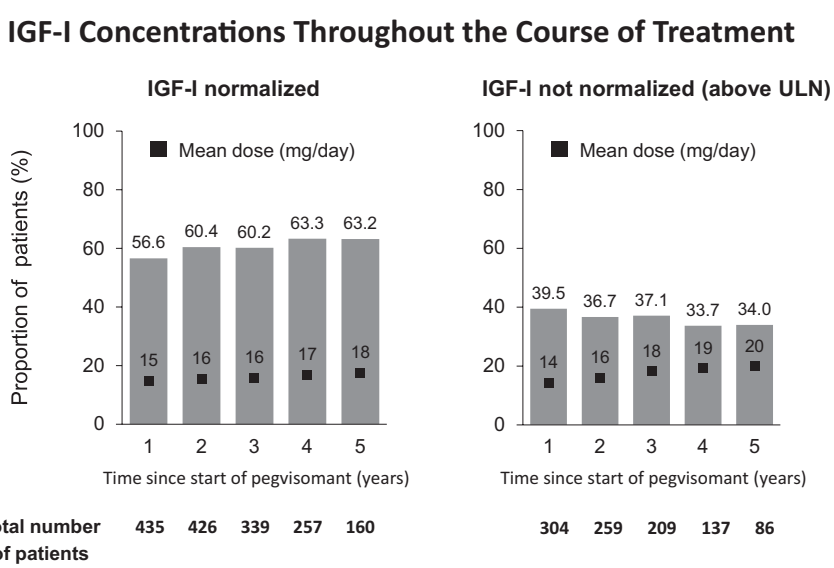

FIG. 2. IGF-I concentrations throughout the course of treatment based on IGF-I levels in local laboratories. n, The actual number of subjects with normalized/nonnormalized IGF-I levels, not the total number of subjects per year of follow-up. The proportion of patients with normal IGF-I levels reported on pegvisomant treatment is shown in the *left panel*, whereas the proportion of patients who did not have normalization of IGF-I is shown in the *right panel*. The mean dose of pegvisomant, expressed as dose per day, is shown *within the bars*.

with AST or ALT elevations reported were using the combination of both pegvisomant and long-acting somatostatin analogs (63.3 *vs.* ~25% for the whole ACROSTUDY population). This is in line with other reports, which suggested that the combination of pegvisomant and somatostatin analogs might increase the risk of AST/ALT elevations by unknown mechanisms (18–20). Important to note is that in all subjects with elevated liver tests and follow-up laboratory results, the increase in AST or ALT had resolved. In a recent report, Bernabeu *et al.* (8) reported that pegvisomant-induced liver injury is related to the UGT1A1*28 polymorphism of Gilbert's syndrome. Although it would be of great interest to investigate this potential link in the ACROSTUDY data set, no analyses on this polymorphism were performed.

There are no recommendations regarding what should be done in subjects with a mild increase in LFT (AST or ALT $< 3 \times$ ULN) during the use of pegvisomant. Close follow-up to ensure reversibility without clinical consequences every 4–8 wk until normalization has been reached might be considered.

Of interest, in 38 subjects, liver-related AE were reported but considered to be unrelated to pegvisomant, highlighting that elevations in liver tests during pegvisomant use could be due to other causes. It is therefore advisable to exclude other potential sources of liver tests elevations, which might need other therapeutic interventions. Importantly, there were no reports of liver failure in this study.

The prevalence of LFT elevations in patients treated with pegvisomant may be higher than found in our study because there may have been some patients with LFT elevations on pegvisomant who had the medication discontinued before enrolment into ACROSTUDY, preventing capture of this AE. Furthermore, elevations of LFT are transient in nature and may not have been documented in the retrospective part of ACROSTUDY.

Another study limitation is that the majority of patients were treated with the medication before enrolling in ACROSTUDY. Medical events that occurred between the pegvisomant start and enrollment into ACROSTUDY were captured as comorbidities and thus lacked rigor typical for AE reporting. An additional limitation of ACROSTUDY is that some degree of AE underreporting might be present. Because of the low frequency of visits within ACROSTUDY per year, AE may have occurred between two visits and therefore not noted or reported by the treating physician.

The third reported side effect is local injection site reactions, most likely induced by an imbalance of the insulin over the (lack of) GH signal (12). In the ACROSTUDY database, 28 investigators reported injection-site reactions, of whom 18 used the terms dystrophy, hypertrophy, or atrophy in their report, indicating that injection-site reactions are infrequent. Frequent rotation of injection sites has been suggested to prevent local reactions (12). A limitation of this study was that details about site rotation were not captured. Mortality in ACROSTUDY was low (1.2%), with no causative role suspected for pegvisomant in any of these cases.

In Europe, pegvisomant is indicated in subjects who are unresponsive or intolerant to somatostatin analogs. We report a pegvisomant efficacy of about 65%, with a calculated dose of around 18 mg/d. This is important because most subjects enrolled were from Europe, meaning they were uncontrolled with other medications before the start of pegvisomant. Because pegvisomant is a competitive GH receptor blocker (21), pharmacology predicts that it should be able to decrease GH signaling into the GH deficiency range, *i.e.* pegvisomant should be able to normalize IGF-I in essentially every patient, provided a high enough dose is administered.

As discussed by Trainer in 2009 (3), the lower-than-expected efficacy of pegvisomant found in ACROSTUDY could be explained by inadequate dosing by the prescrib-

ing physicians or inadequate patient compliance. These could be based on lack of knowledge or economic reasons that differ by country. It is also possible that some patients chose not to elevate the dose above 20 mg/d because that would have required two daily injections with the currently available formulation. There are several other possible explanations for the efficacy differences between early clinical trials and this ACROSTUDY report.

The original studies by Trainer *et al.* and van der Lely and colleagues (1, 2) used a different criterion to assess IGF-I normalization. In those reports, if a patient had even a single IGF-I level within the normal reference range at least once during the whole follow-up period, this was classified as normalization of IGF-I. In contrast, in the current study, IGF-I normalization was evaluated on a yearly basis. Second, the assay used in the previous studies was the old Nichols assay, which is no longer available. The Immulite assay widely used currently is known to yield higher IGF-I levels compared with the prior Nichols assay (22). Using the Immulite assay, some patients classified in the normalized group in the original studies would have been considered uncontrolled in ACROSTUDY. Furthermore, ACROSTUDY is a noninterventional, phase IV registry study assessing long-term safety, representing real-life clinical care in the practice setting; this is very different from the standardized protocols evaluating efficacy with specific visit intervals, treatment schedules/dosing, and centralized laboratories used in clinical trials. Finally, because the proportion of normalized patients in ACROSTUDY is stable over time without an increase in pegvisomant dose, tachyphylaxis does not appear to play a role. Moreover, no participating center in ACROSTUDY has reported tachyphylaxis. Whether drug adherence plays an additional role in the different efficacy observed in ACROSTUDY compared with early reports is unknown because adherence was not assessed in ACROSTUDY.

Although the observed efficacy in ACROSTUDY is lower than the original reports, these data support the conclusions of recent consensus reports (23, 24). In these guidelines, pegvisomant is suggested for patients with persistently elevated IGF-I levels despite maximal therapy with other treatment modalities. Our analyses of ACROSTUDY show that pegvisomant can control IGF-I levels in a majority of patients with acromegaly who do not respond adequately to other therapies.

In conclusion, ACROSTUDY is a valuable tool in the assessment of the long-term safety of pegvisomant in the treatment of acromegaly. Data entered in ACROSTUDY up to December 31, 2009, on 1288 subjects indicate that pegvisomant is an effective and safe medical treatment in patients with acromegaly who cannot be controlled by somatostatin analog monotherapy. Although there are limitations in ACROSTUDY, the low rates of pituitary tumor enlargement, liver test elevations, and injection-site reactions in this global, noninterventional, surveillance study are reassuring. In the future, additional data on more patients for longer duration will provide further information about the treatment of this rare condition.

Acknowledgments

We thank all of the investigators, subinvestigators, nurses, and study coordinators involved in ACROSTUDY and the patients who allowed their data to be captured. ACROSTUDY is sponsored by Pfizer Inc. We also thank Dr. Pia Burman for her significant contribution to the design of the ACROSTUDY and for her valuable help with evaluating the data.

Address all correspondence and requests for reprints to: A. J. van der Lely, M.D., Department of Internal Medicine, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: a.vanderlelij@erasmusmc.nl.

Disclosure Summary: A.J.v.d.L., B.M.K.B., T.B., M.B., E.G., C.J.S., and S.M.W. receive honoraria from Pfizer as members of the ACROSTUDY Strategic Advisory Board. R.G., J.H.-H., F.L., N.R., and M.K.-H. are permanent employees of Pfizer. The authors were not paid for their contribution to this manuscript.

References

1. **Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, Dimaraki EV, Stewart PM, Friend KE, Vance ML, Besser GM, Scarlett JA, Thorner MO, Parkinson C, Klibanski A, Powell JS, Barkan AL, Sheppard MC, Malsonado M, Rose DR, Clemmons DR, Johannsson G, Bengtsson BA, Stavrou S, Kleinberg DL, Cook DM, Phillips LS, Bidlingmaier M, Strasburger CJ, Hackett S, Zib K, Bennett WF, Davis RJ** 2000 Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med 342:1171–1177
2. **van der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, Klibanski A, Herman-Bonert V, Melmed S, Vance ML, Freda PU, Stewart PM, Friend KE, Clemmons DR, Johannsson G, Stavrou S, Cook DM, Phillips LS, Strasburger CJ, Hackett S, Zib KA, Davis RJ, Scarlett JA, Thorner MO** 2001 Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet 358:1754–1759
3. **Trainer PJ** 2009 ACROSTUDY: the first 5 years. Eur J Endocrinol 161(Suppl 1):S19–S24
4. **Brue T, Castinetti F, Lundgren F, Koltowska-Haggström M, Petrossians P** 2009 Which patients with acromegaly are treated with pegvisomant? An overview of methodology and baseline data in ACROSTUDY. Eur J Endocrinol 161(Suppl 1):S11–S17
5. **Gutíerrez LP, Koltowska-Häggström M, Jönsson PJ, Mattsson AF, Svensson D, Westberg B, Luger A** 2008 Registries as a tool in evidence-based medicine: example of KIMS (Pfizer International Metabolic Database). Pharmacoepidemiol Drug Saf 17:90–102
6. **van der Lely AJ, Bernabeu I, Cap J, Caron P, Colao A, Marek J, Neggers S, Birman P** 2011 Coadministration of lanreotide Autogel and pegvisomant normalizes IGF1 levels and is well tolerated in patients with acromegaly partially controlled by somatostatin analogs alone. Eur J Endocrinol 164:325–333

7. **Buhk JH, Jung S, Psychogios MN, Göricke S, Hartz S, Schulz-Heise S, Klingebiel R, Forsting M, Brückmann H, Dörfler A, Jordan M, Buchfelder M, Knauth M** 2010 Tumor volume of growth hormone-secreting pituitary adenomas during treatment with pegvisomant: a prospective multicenter study. J Clin Endocrinol Metab 95:552–558
8. **Bernabeu I, Marazuela M, Lucas T, Loidi L, Alvarez-Escolá C, Luque-Ramírez M, Fernandez-Rodriguez E, Paniagua AE, Quinteiro C, Casanueva FF** 2010 Pegvisomant-induced liver injury is related to the UGT1A1*28 polymorphism of Gilbert's syndrome. J Clin Endocrinol Metab 95:2147–2154
9. **Buchfelder M, Weigel D, Droste M, Mann K, Saller B, Brübach K, Stalla GK, Bidlingmaier M, Strasburger CJ** 2009 Pituitary tumor size in acromegaly during pegvisomant treatment: experience from MR re-evaluations of the German Pegvisomant Observational Study. Eur J Endocrinol 161:27–35
10. **Neggers SJ, van Aken MO, Janssen JA, Feelders RA, de Herder WW, van der Lely AJ** 2007 Long-term efficacy and safety of combined treatment of somatostatin analogs and pegvisomant in acromegaly. J Clin Endocrinol Metab 92:4598–4601
11. **Frohman LA, Bonert V** 2007 Pituitary tumor enlargement in two patients with acromegaly during pegvisomant therapy. Pituitary 10: 283–289
12. **Bonert VS, Kennedy L, Petersenn S, Barkan A, Carmichael J, Melmed S** 2008 Lipodystrophy in patients with acromegaly receiving pegvisomant. J Clin Endocrinol Metab 93:3515–3518
13. **Hodish I, Barkan A** 2008 Long-term effects of pegvisomant in patients with acromegaly. Nat Clin Pract Endocrinol Metab 4:324–332
14. **Buchfelder M, Schlaffer S, Droste M, Mann K, Saller B, Brubach K, Stalla GK, Strasburger CJ** 2009 The German ACROSTUDY: past and present. Eur J Endocrinol 161(Suppl 1):S3–S10
15. **Schreiber I, Buchfelder M, Droste M, Forssmann K, Mann K, Saller B, Strasburger CJ** 2007 Treatment of acromegaly with the GH receptor antagonist pegvisomant in clinical practice: safety and efficacy evaluation from the German Pegvisomant Observational Study. Eur J Endocrinol 156:75–82
16. **Colao A, Pivonello R, Auriemma RS, De Martino MC, Bidlingmaier M, Briganti F, Tortora F, Burman P, Kourides IA, Strasburger CJ, Lombardi G** 2006 Efficacy of 12-month treatment with the GH receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose somatostatin analog treatment: effect on IGF-I levels, tumor mass, hypertension and glucose tolerance. Eur J Endocrinol 154:467–477
17. **Higham CE, Chung TT, Lawrance J, Drake WM, Trainer PJ** 2009 Long-term experience of pegvisomant therapy as a treatment for acromegaly. Clin Endocrinol 71:86–91
18. **Neggers SJ, van der Lely AJ** 2011 Combination treatment with somatostatin analogues and pegvisomant in acromegaly. Growth Horm IGF Res 21:129–133
19. **Neggers SJ, van der Lely AJ** 2009 Somatostatin analog and pegvisomant combination therapy for acromegaly. Nat Rev Endocrinol 5:546–552
20. **Neggers SJ, de Herder WW, Janssen JA, Feelders RA, van der Lely AJ** 2009 Combined treatment for acromegaly with long-acting somatostatin analogs and pegvisomant: long-term safety for up to 4.5 years (median 2.2 years) of follow-up in 86 patients. Eur J Endocrinol 160:529–533
21. **Kopchick JJ, Parkinson C, Stevens EC, Trainer PJ** 2002 Growth hormone receptor antagonists: discovery, development, and use in patients with acromegaly. Endocr Rev 23:623–646
22. **Trainer PJ, Ezzat S, D'Souza GA, Layton G, Strasburger CJ** 2009 A randomized, controlled, multicentre trial comparing pegvisomant alone with combination therapy of pegvisomant and long-acting octreotide in patients with acromegaly. Clin Endocrinol (Oxf) 71: 549–557
23. **Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, Clemmons D, Chanson P, Laws E, Schlechte J, Vance ML, Ho K, Giustina A, Acromegaly Consensus G** 2009 Guidelines for acromegaly management: an update. J Clin Endocrinol Metab 94:1509–1517
24. **Melmed S** 2009 Acromegaly pathogenesis and treatment. J Clin Invest 119:3189–3202