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Safety of long-term treatment with Pegvisomant: analysis of Spanish patients included in global ACROSTUDY

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Abstract
Purpose To evaluate the long-term safety of Pegvisomant (PEG) in the Spanish cohort of ACROSTUDY.
Methods As of July 2013, 199 Spanish patients were included in ACROSTUDY, a global non interventional safety PEG surveillance study. Patients were observed for safety, biochemical outcome and magnetic resonance imaging evaluations.
Results PEG was administered during an average period of 6.7 ± 2.1 years and a mean daily dose of 15.5 ± 7.5 mg. 48.2 % of patients received PEG monotherapy. 90.9 % of patients had received other medical treatment before PEG start. 195 adverse events (AEs) were reported in 88 patients (44.2 %), and serious AEs were described in 31 patients (15.6 %). There were no cases of liver tests >10 ULN, or permanent liver damage. Tumor size changes were locally reported in 61 cases (33.5 %), with increases observed in 11 patients (6 %). In acromegalic patients with diabetes mellitus a decrease in fasting serum glucose value was reported, reaching statistical significance after 1 and 4 years of treatment (−24.6 and −25.9 mg/dl, $p = 0.04$). After 60 months, normal or lower limit of normal (LLN) IGF-I levels were found in 67.9 % of patients. 85.5 % of patients showed an IGF-I normal or <LLN at any time after PEG start. Most patients with uncontrolled IGF-I levels were on submaximal PEG doses.
Conclusions ACROSTUDY carried out with the Spanish cohort confirmed that PEG has a favorable safety and efficacy profile. The percentage of patients considered under control was similar to data reported globally and in other local ACROSTUDY results.

Keywords Acromegaly · Pegvisomant · ACROSTUDY · Safety · IGF-I

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Introduction

Pegvisomant (PEG) (Somavert®, Pfizer), a genetically engineered GH analogue with growth hormone receptor (GHR) antagonist properties, was approved by the European Medicines Agency on November 2002 for those patients who have not achieved a biochemical control of the disease after surgery and are resistant to somatostatin analogs (SSA) treatment. Recently, FDA has reviewed the indication of second line of treatment, considering in some patients PEG could be used as first line of medical therapy. Pivotal studies with PEG showed a high therapeutic efficacy by normalizing IGF-I level during follow-up in up to 95 % of patients with a favorable safety profile: injection

site reactions, liver dysfunction and two cases with increased tumor size were its main adverse events [1–3].

PEG produces an increase in GH secretion, reaching a plateau after the first few weeks of therapy, because of a reduced IGF-I feedback or from a direct effect on the pituitary [1, 2]. When PEG was commercialized there were some concerns regarding whether the GH hypersecretion could cause growth of the residual tumor or the overcoming of receptor blockade with loss of efficacy. Additionally, the possibility that the development of specific antibodies against PEG would cause a loss of long-term efficacy had not been adequately evaluated [4]. PEG commercialization was followed by the onset of two main observational surveillance studies aiming to evaluate the safety and outcome of long-term PEG treatment: the German Pegvisomant Observational Study (GPOS) [5–9], and shortly thereafter ACROSTUDY [10, 11], sponsored by Pfizer. Eventually, most cases included in GPOS study were merged into the ACROSTUDY global database. Data from a growing number of acromegaly patients enrolled into the ACROSTUDY are periodically reported [10–16]. In this study, we present data from Spanish patients included in global ACROSTUDY with up to 9 years of follow-up.

Patients and methods

At the data freeze on July 2013, 199 Spanish patients from 41 centers were included in the ACROSTUDY. Data were collected using electronic web-based Case Report Forms (eCRF). Inclusion criteria restricted to patients with acromegaly who were already treated or about to start treatment with PEG. Exclusion criteria included patients under 18 years, or participating in any clinical trial of an investigational drug for acromegaly, or requiring surgical decompression of a tumor or who should have nonmedical therapy because of visual field loss related to a tumor contact with the optic chiasm, cranial nerve palsies, or intracranial hypertension.

The collected information included personal data (age, gender), physical examination (height, weight, blood pressure), time of first diagnosis of acromegaly, time of PEG therapy start, time of inclusion in ACROSTUDY, previous and current therapy, concomitant medication, co-morbidities, visual fields, IGF-I levels, pituitary function, pituitary imaging studies, liver function tests (ALT, AST, GGT), fasting blood glucose and HbA1c (diabetic patients only) and symptoms during the study (following a patient-assessed acromegaly symptom questionnaire, PASQ). Diabetes mellitus diagnosis was assumed in all patients chronically treated with hypoglycemic drugs. In those patients previously diagnosed with diabetes mellitus but without any kind of hypoglycemic drug and in all new cases, the diagnosis was documented according to American Diabetes Association criteria.

All biochemical studies, including IGF-I, were performed locally and reported in relation to local reference values. MRI examinations were performed and interpreted locally. Changes in tumor size larger than 20 % (volume) or more than 3 mm in the largest diameter, were considered significant. When required, MRI scans were re-evaluated in a central reference unit. Adverse events (AE) were defined as any unfavorable medical observation, regardless of potential relationship to PEG treatment. Serious AEs (SAEs) were considered those that were fatal or life threatening, required hospitalization, or prolongation of existing hospitalization, resulted in in utero exposure or produce permanent or serious disability/incapacity.

The study was conducted in compliance with the Declaration of Helsinki and was approved by Puerta de Hierro Hospital ethic committee. All patients signed an informed consent before enrollment into ACROSTUDY.

Statistical analyses

Statistical analyses were performed using the Statistical Analysis System (SAS 9.2). Descriptive data are presented as mean ± standard deviation (SD) unless otherwise indicated. Comparisons within groups were analyzed with the Wilcoxon sign-rank test and significance was accepted at $p < 0.05$.

Results

Patient characteristics

The study comprises 199 patients from 41 centers recruited in the Spanish ACROSTUDY from start in 2004 until July 2013. A summary of patients demographic characteristics is presented in Table 1. The population was mostly Caucasian (99 %) with a slightly higher contribution of women (57.3 %) and an average age at diagnosis of 43.3 ± 13.9 years. The mean duration of acromegaly before PEG start was 6.4 ± 7.0 years with 9.0 % of patients initiating treatment in the first year of diagnosis and 39.7 % after more than 5 years. Before initiation of PEG medication, 90.9 % of patients had already received other medical treatment; only on 7 individuals (3.5 %), no previous treatment was reported (Fig. 1).

Thirty-two patients (16.1 %) did not have any co-morbidities at treatment start. New co-morbidities recorded before and after PEG starts were similar. The most prevalent co-morbidities before PEG and between PEG and

Table 1 Demographic Characteristics of 199 patients from Spanish ACROSTUDY

	Male	Female	All
Number (%)	85 (42.7)	114 (57.3)	199 (100)
Age (years) at diagnosis of acromegaly, mean (SD)	38.9 (11.7)	46.5 (14.5)	43.3 (13.9)
BMI (kg/m^2), mean (SD)	28.5 (4.31)	29.4 (4.13)	29.1 (4.14)
Duration (years) of acromegaly before PEG start, mean (SD)	7.1 (7.7)	5.9 (6.4)	6.4 (7)
Age (years) at PEG start., mean (SD)	45.9 (11.9)	52.4 (15.3)	49.6 (14.3)
Years on PEG, mean (SD)	6.9 (2)	6.6 (2.1)	6.7 (2.1)
Years in ACROSTUDY, mean (SD)	5.5 (1)	4.8 (1.1)	4.9 (1)

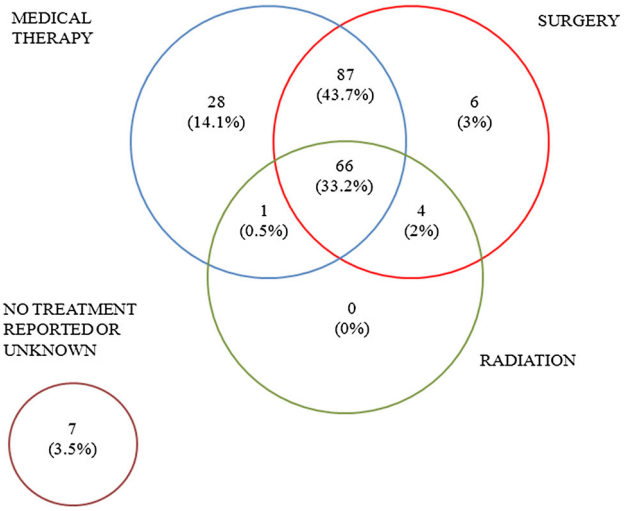

Fig. 1 Treatment modalities used prior to initiation of PEG

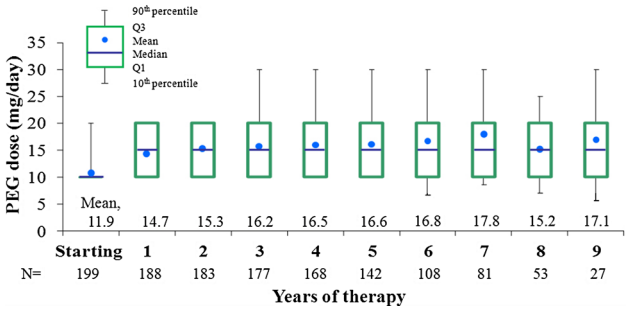

Fig. 2 Daily PEG doses during the study

ACROSTUDY were respectively: cardiovascular (mostly hypertension) 53.3 % and 26.2 %; metabolic (diabetes mellitus) 37 % and 9.5 %; musculoskeletal (mainly osteoarthritis) 35.2 % and 9.5 %; tumors (thyroid and colon with higher incidence) 29.7 % and 31 %; respiratory (sleep apnea principally) 19.4 % and 9.5; liver gallbladder 11.5 %; and 2.4 %; goiter 6.7 % and 2.4 %; and cerebrovascular 2.4 % and 0 %. According to the protocol, all disorders with onset after ACROSTUDY start were reported as adverse events.

PEG was administered during an average period of 6.7 ± 2.1 years, and the mean follow-up in ACROSTUDY was 4.9 ± 1.1 years. Only 48.2 % of patients received PEG monotherapy and 97.5 % of patients took PEG daily. PEG doses were titrated according to the individual patient situation, following treating physician's judgment. The mean daily dose (mg) of PEG during the study was 15.5 ± 7.5, ranging between 14.7 ± 6.6 in the first year and 17.9 ± 9.1 at the seventh year of follow-up (Fig. 2). BMI remained without significant changes during therapy with PEG (Table 1). According to patient weight (mg/kg), women received higher PEG doses than men did.

Treatment outcomes

Safety analysis

ACROSTUDY, as a non-interventional surveillance study, was designed with the primary intention to provide medical information about safety on long-term "real-life" PEG treatment. All causalities AE (Table 2) were reported in 88 (44.2 %) patients and were similar to those described in the global ACROSTUDY. SAEs were described in 31 (15.6 %) patients and 10 (5 %) patients died although in none of them the death was related to treatment. In 23 (11.6 %) and in 3 (1.5 %) cases, AE and SAE, respectively, were considered potentially related to PEG (Table 3). However, only in two cases (1 %) PEG was discontinued because of the SAE: one case with failure to response to treatment and another case with a recurrence of the pituitary tumor. In no case, the dose of PEG was reduced because of an AE and there were no relationships between AE/SAE and dose or duration of PEG treatment.

All causalities and treatment-related AE included several disorders: 3 cases of blood disorders, 6 cardiac, 7 endocrine, 2 ophthalmic, 12 gastrointestinal, 31 related to deregulated biochemical parameters (glucose, GH, liver transaminases…), 10 metabolic, 12 musculoskeletal, 8 neoplasm, 13 neurological, 6 psychiatric, 5 renal and urinary, 2 hepatobiliary, 10 respiratory, 7 vascular, 3 affecting the skin, 1 hydrocele, 1 pneumonia, 1 drug hypersensitivity and 2 fractures (femur and hip). Five patients required

Table 2 Summary of AE and number of deaths in 199 patients on treatment with PEG followed during 9 years

Adverse events (AE)	Patients (%)
AE (all causality)	88 (44.2)
AE (related to treatment)	23 (11.6)
Serious AE (SAE)	31 (15.6)
SAE related to treatment	3 (1.5)
Treatment discontinuation due to SAE	16 (8)
Treatment discontinuation due to SAE related to treatment	2 (1)
Dose reduced due to SAE	0 (0)
Deaths	10 (5)
Deaths consider related to treatment	0 (0)

Table 3 AE potentially related to treatment and PEG discontinuation due to a SAE

Adverse event	AE n (%)	SAE n (%)
Patients	23 (11.6)	3(1.5)
Investigations	15 (7.5)	
GH increased	1	
IGF-I increased	15	
General disorders	1 (0.5)	1 (0.5)
No therapeutic response	1	1[a]
Nervous system disorders	2 (1)	
Headache	2	
Gastrointestinal disorders	1 (0.5)	
Abdominal pain	1	
Neoplasms benign, malignant and unspecified	1 (0.5)	1 (0.5)
Pituitary tumor recurrence	1	1[a]
Administration site conditions and skin disorders	2 (1)	1 (0.5)
Injection site reaction	1 (0.5)	
Lipohypertrophy	1 (0.5)	1
Not coded	1 (0.5)	

[a] Treatment discontinuation

surgical intervention: one cataract operation, two cholecystectomies, one hip surgery and one vertebroplasty. Death occurred in 10 (5 %) patients but none were considered to be related to PEG treatment. The main characteristics of this group of patients are detailed in Table 4.

Liver function

Significant increased liver function tests (ALT/AST $\geq 3\times$ ULN or FAL/BIL/g-GT/$>1\times$ ULN) were reported in 14 (7 %) patients. In seven of them, liver dysfunction was present before PEG treatment. Among the remaining 7 cases, 4 presented with FAL no higher than $1.1\times$ ULN. Only 3 (1.5 %) patients presented ALT or AST levels $>3\times$ ULN. There were no cases of transaminases higher than $10\times$ ULN. In no case, liver dysfunction was considered as related to PEG treatment or required drug withdrawal.

Pituitary tumor size

Pituitary tumor size was evaluated by MRI in 182 out of 199 patients (91.5 %). Changes in tumor size were locally reported in 61 (33.5 %) cases after PEG start. An increase in tumor size was observed in 11 (6 %) cases, a decrease in 45 (24.7 %) cases and both increase and decrease in 5 (2.7 %) cases (Fig. 3). Among 11 cases with a tumor volume increase, none was surgically treated during the year previous to MRI examination data. Five of these patients were receiving PEG in monotherapy and six in combination with somatostatin analogs or dopamine agonists. Twenty-five out of the 45 cases with decrease in tumor size during the follow-up had been previously treated with radiation therapy. Moreover, in this group 22 patients (48.9 %) were on PEG monotherapy and 23 (51.1 %) were in combined treatment. Finally, all cases

Table 4 Cause of mortality, dose and duration of PEG treatment and causality

Sex	Age	Cause of death	PEG dose	Years on PEG treatment	PEG causality
Male	64	Respiratory failure (pneumonia)	20	7.1	No
Male	55	General disorder (unspecified)	30	4.4	No
Female	82	Myocardial infarction/heart failure	UK	3.8	No
Female	67	Fever an decreased level of consciousness	10	4.8	No
Female	73	Aortic aneurism rupture	20	5.5	No
Female	70	Cerebrovascular stroke	20	6.7	No
Female	73	Thyroid papilary carcinoma	30	5.7	No
Female	63	General disorder (unspecified)	20	5.6	No
Female	77	Cardiac sudden death	10	5.7	No
Female	66	Heart failure	40	4	No

UK unknown

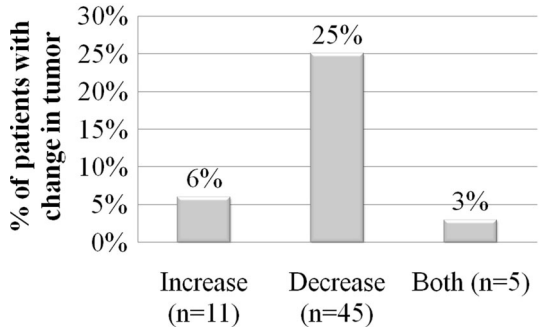

Fig. 3 Changes in tumor size from baseline during follow up based on local MRI reading

with both increase and decrease in tumor size were on combined treatment and 4 of them had been previously treated with radiotherapy.

Diabetes mellitus

At baseline, diabetes mellitus was documented in 61 (30.7 %) patients. The diabetic group was compared to the non-diabetic group. The percentage of IGF-I normalization was not different between both groups, although diabetic patients' required higher PEG doses to normalize IGF-I (Fig. 4).

Diabetes mellitus was treated with diet and lifestyle modification in 17 and 21 cases at the start and at the end of follow-up; with insulin therapy in 17 and 11; with other pharmacological agents [oral agents and glucagon-like-peptide-1 (GLP) agonist] in 22 and 12 cases and with a combination of oral drugs and GLP-1 agonists in 5 and 17 cases respectively.

In the DM group, PEG treatment was followed by a better glucose control. The mean change in fasting glucose levels from baseline at year 1 and 4, were statistically

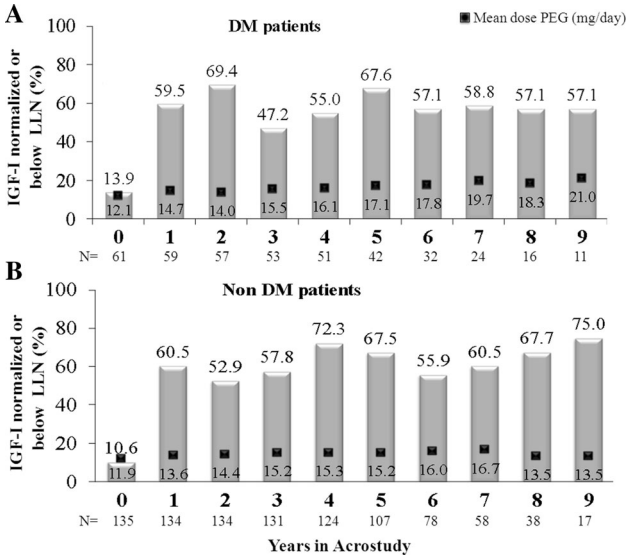

Fig. 4 Percentage of IGF-I normalization and PEG dose (mg/day) throughout the course of treatment in patients with (*A*) and without (*B*) diabetes mellitus (DM) (cross-sectional data)

significant (−24.6 and −25.9 mg/dl, respectively; $p < 0.04$ for both; data not shown). HbA1c level was available in only few cases, so statistical evaluation was not valuable.

Efficacy

Before PEG treatment, 11.8 % of the studied population had normalized IGF-I levels. On PEG treatment up to 85.5 % of patients reached a serum IGF-I concentration normal or below the lower level of normal (LLN), at least once during the follow-up period. Throughout the course of treatment, the percentage of patients with IGF-I normal or below LLN, ranged from 60.2 % of patients assessed after 12 months (n = 113) to 67.9 % of patients assessed after

60 months (n = 112). As of July 2013, 15 patients reached 9 years of follow-up, 66.6 % of them with controlled IGF1. The mean daily dose (mg) of PEG at last observation was 15.2 ± 1.1 for patients with normal or below LLN IGF-I levels (N = 112) and 17.6 ± 1.6 for the uncontrolled group (N = 77) (Fig. 5). In the group of patients treated with PEG monotherapy, mean daily doses (mg) ranged between 8.1 ± 2.2 and 14.3 ± 6.7 in controlled patients and between 10.3 ± 1.2 and 18.3 ± 6.5 in the uncontrolled group. The percentage of IGF-I normalization (IGF-I normal or below LLN) in monotherapy group ranged from 59 % after 36 months (n = 61) to 76.2 % after 48 months (n = 63).

Discussion

ACROSTUDY is a phase IV non-interventional surveillance trial launched in 2004 and intended to provide information about long-term safety and outcomes of PEG treatment for acromegaly. Currently, ACROSTUDY involves more than 1800 patients from 15 countries. Several interim global reports have been published [10–15], but only data from two national cohorts, Germany and Italy, have been presented [5, 6, 16]. Taking into account that ACROSTUDY reflects actual clinical practice in each country, national reports within the global project may help us to identify variations in clinical practice and standard of care or characteristics of a local population that may give us some clues to improve manage of the disease and its outcome.

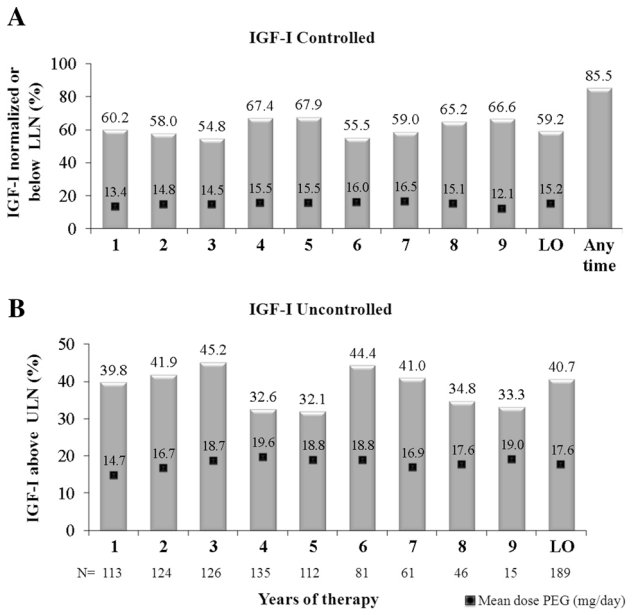

Fig. 5 Percentage of patients with IGF-I normalization (*A*) or above ULN (*B*) and PEG dose (mg/day) throughout the course of treatment (cross-sectional data)

The Spanish cohort comprises 199 patients, which accounts for more than 10 % of the global study population. A summary of published reports from ACROSTUDY and former projects (GPOS and Clinical Trials) is shown in Tables 5 and 6. As expected, most characteristics remained in line with global reports. However the Spanish enrolled population was younger (around 7 years) with a higher representation of women (57.3 %). These features are in accordance with previous epidemiological studies of acromegaly in Spain [17, 18].

In this study with the longest published follow-up (mean 6.7 ± 2 years and up to 9 years in some patients), we did not find an increased frequency of safety issues. Adverse events were reported in 44.2 % of patients and were not related with PEG dose or treatment duration. 11.6 and 1.5 % of patients developed AE or SAEs (lipohypertrophy, pituitary tumor recurrence and an absence of therapeutic response) related with treatment. Only in these two last cases (1 %) PEG therapy was discontinued. There was no mortality related to PEG treatment. We found four cases of injection site reaction; three of them described as lipohypertrophy (2) or lipodystrophy (1), representing a prevalence of 1.5 %, similar to that reported in the last analysis of global ACROSTUDY [17, 18]. All injection site reactions resolved without treatment discontinuation. Significant increased liver function tests (ALT/AST ≥3× ULN or FAL/BIL/g-GGT/≥1× ULN) were reported in 14 (7 %) patients, however only 3 patients (1.5 %) showed ALT/or AST levels higher than 3× ULN. The prevalence of liver dysfunction in this series was similar to that described in the global ACROSTUDY and lower than the one described in German and Italian cohorts (Table 6). This lower prevalence in the Spanish cohort is difficult to explain but could be related to less frequent communication of mild and transient alterations in liver function tests by Spanish investigators or to a lower incidence of other risk factors for liver dysfunction as the presence of previous liver disease or the use of combined PEG plus somatostatin analogues treatment or polypharmacy [19–21].

The possibility that GH hypersecretion secondary to PEG treatment would lead to the growth of residual tumor has been the main concern of PEG treatment. However the overall percentage of tumor growth during PEG treatment is not different to that described for other treatment modalities of acromegaly [14, 15, 22] and in most cases, when occurs, the tumor growth was mild and clinically non-significant [23].

In our series, we found 11 cases of tumor growth (6.0 %) locally reported. Only in one case, the responsible investigator considered tumor growth as a SAE probably related with PEG treatment, which was discontinued.

Table 5 Summary of PEG studies: patients, treatments and outcome

Reference	Country	Period	Treatment (years)	Patients (women)	Patients age (years)	Previous medical therapy	Surgery	Radiation therapy	Surg + RTh	Average dose (mg/d)	Monother	IGF-I below ULN
Stewart [41] (Clinical Trial review)	NA	1 year	1	160 (66)	46 ± 14	NA	84 %	59 %	NA	18	NA	97 %
Schreiber et al. [5] (GPOS)	Germany	2004–2006	4.3 ± 3.0	229 (111)	NA	94.3 %	90.4 %	43.2 %	NA	16.5 ± 7.7	NA	76.3 %
Brue [13] (ACROSTUDY)	10	2004–2008	4	469 (228)	Around 50	80.0 %	77 %	35 %	NA	18.7–22.0	67 %	62–78 %
Trainer [10] (ACROSTUDY)	10	2004–2009	3.3	792 (390)	51.3	86.0 %	48.9 %	2.4 %	30.4 %	NA	67 %	<70 %
van der Lely et al. [14] (ACROSTUDY)	12	2004–2009	3.7	1288 (631)	49.8	87.8 %	74.1 %	28.1 %	2.0 %	18.0	NA	63.2 %
Buchfelder et al. [6] (ACROSTUDY)	Germany	2004–2008	9.8 ± 6.7	371 (186)	50.0 ± 14.0	89.1 %	89.4 %	42.2 %	NA	16.4 ± 8.5	79.8 %	58.4–71.3 %
Grottoli et al. [16] (ACROSTUDY)	Italy	2004–2012	4.3 ± 2.5	341 (170)	50.4 ± 14.2	93.0	54.3 %	NA	15.8 %	18.1	41.9 %	70.9 %
Bernabeu et al. (current study) (ACROSTUDY)	Spain	2004–2013	6.7 ± 2.1	199 (114)	43.4 ± 13.9	77.6 %	81.9 %	35.7	35.2	15.5 ± 7.5	48.2 %	85.5 %

NA not available, *Surg* surgery, *RTh* radiotherapy, *Monother* Monotherapy

Although in the remaining 10 cases is not possible to know the reason for tumor growth, the fact that they were not considered as SAE and PEG treatment was continued suggests their slight or mild clinical significance as previously reported [23, 24]. These findings are similar to those in the interim global ACROSTUDY and other national reports (Table 5).

The percentage of IGF-I normalization in our study using the *latest IGF-I criteria* (IGF-I normalization at the end of study or at predefined time) (67.9 % at 5 years follow-up) (Fig. 5) was similar to that described in the German and Italian series and the global study [5, 14, 16]. Nevertheless and using the *lowest IGF-I criteria* (IGF-I normalization at least once during follow-up) our values rise to 85.5 %, approaching to the values reported (89–97 %) in pivotal studies [1, 14].

PEG doses used in our study were lower than in the German, Italian and global studies, both in controlled (15.2 vs 17.5, 18.1 and 18 mg/day, respectively) and in uncontrolled patients (17.6 vs 22.5, 22.3 and 20 mg/day, respectively) [5, 14–16]. The similar efficacy of PEG in spite of the use of lower doses are probably partially related to different and varying biochemical response to combined treatment (SSA and/or cabergoline) that 52 % of included patients were receiving. Also, differences in compliance and in some additional factors recently described [25] contributing to uncontrolled IGF-I may be involved. Finally, we cannot rule out that some patient or country specific characteristics or perhaps different prevalence of some genotypic variations recently described [26–30] may underlie this difference in the required dose of PEG. In this study the disease was out of control in 32.1–45.2 % of the patients throughout the follow-up. PEG dose in this uncontrolled group was lower than maximum approved doses that had been used in the pre-commercialization studies and even so, the IGF-I levels showed a downward trend through the study suggesting a failure of dose titration and not ineffectiveness of the drug. Probably the percentage of controlled acromegalic patients should have been significantly higher if higher doses of PEG had been used, without an increase in AE. In a previous Spanish long-term study performed in a clinical setting, the percentage of IGF-I normalization reached 84 % with a mean PEG daily dose of 17.7 ± 7 mg [31]. So, a stricter dosing regimen and follow-up protocol must be warranted.

According to previous reports [31, 32], the Spanish women with acromegaly, required higher PEG doses per kilogram (0.041 mg/kg) than men to achieve a similar IGF-I goal, but some or most of the acromegalic women could be on estrogen replacement therapy. The liver is a sex steroid-responsive organ, as well as the metabolism and the principle source of IGF-I. Many aspects of hepatic function are perturbed by supra-physiological

Table 6 Summary of PEG studies: safety

Reference	AE general	AE treatment associated	SAE general	SAE treatment associated	Discont. (all causes)	Discont treat. associated	Liver dysfunction (TA)	Skin reactions	Tumor size increase	Confirmed increase	Tumor size decrease	Tumor size in and dec.	Mortality
Stewart [41] (Clinical Trial review)	NA	NA	NA	NA	NA	NA	1.3 %	11.3 %	1.3 %	NA	NA	NA	NA
Schreiber et al. [5] (GPOS)	48.9 %	21.8 %	NA	11.8 %	7.9 %	NA	5.2 %	7.4 %	5.2 %	3.1 %	NA	NA	NA
Brue [13] (ACROSTUDY)	13.0 %	NA	NA	1.3 %	NA	1.3 %	7.7 %	NA	5.1 %	NA	NA	NA	NA
Trainer [10] (ACROSTUDY)	17.9 %	7.1 %	5.8 %	1.6 %	NA	NA	3.7 %	1.1 %	2.8 %	2.8 %	3.9 %	1.4 %	NA
van der Lely et al. [14] (ACROSTUDY)	37.0 %	9.6 %	12.3 %	2.0 %	1.7 %	0.3 %	2.5 %	2.2 %	7.2 %	3.2 %	12.6 %	1.4 %	1.2 %
Buchfelder et al. [6] (ACROSTUDY)	NA	NA	NA	NA	10.9 %	6.7 %	5.4 %	3.2 %	5.4 %	3.1 %	NA	NA	NA
Grottoli et al. [16] (ACROSTUDY)	28.7 %	NA	8.5 %	0.6 %	NA	5.6 %	8.4 %	0.3 %	8.8 %	2.1 %	13.7 %	6.4 %	NA
Bernabeu et al. (current study) (ACROSTUDY)	44.2 %	23 %	31 %	3 %	16 %	2 %	14 %	1.5 %	6 %	NA	24.7	2.7 %	10 %

AE adverse effects, *SAE* serious adverse effects, *TA* elevated liver transaminases (>3xULN), *Discont* discontinuation, *in and dec* increase and decrease, *NA* not available

concentrations of estrogen in the portal circulation after oral administration. This effect results in a major site of GH-regulated stimulation of the synthesis of the binding proteins for several steroid hormones and GHBP. Recent evidence has emerged that estrogens exert profound effects on this component of GH/IGF-I physiology in a route-dependent manner [33]. Therefore, the increase of liver GH receptors during estrogen replacement therapy could explain the higher PEG doses required by women respect to men in our study and other ones.

Diabetic patients (n = 61) showed a significant improvement of glycemic control as has been previously described [14]. The amelioration of glycemic control should be attributed to the blockade of the contra-insular effects of GH, reducing the hepatic production of glucose. Paradoxically, diabetic acromegalic patients required higher PEG doses (Fig. 4) to achieve IGF-I normalization. According to recent reports [34, 35] this effect is presumably related to hyperinsulinism. Insulin enhances growth hormone–stimulated synthesis of IGF-I and IGFBP-3 through up-regulation of growth hormone receptors [36, 37]. So, hyperinsulinemic diabetic patients (especially insulin treated ones) could exhibit an increased expression of hepatic GHR [38–40], thus requiring higher concentrations of PEG for full receptor blockage.

The present study has some limitations. The retrospective nature impaired the possibility to obtain complementary data. Heterogeneity of patients, time of therapy start, follow-up period, complementary therapies, diversity of professionals and centers make the analysis complex and hinder the achievement of clear-cut conclusions. However, these apparent limitations are an advantage since they reflect real clinical practice and its similarities with the other studies reported allow us to be very confident with our results. The long-term follow-up period of more than 9 years, give an additional value to this study.

To conclude, this non interventional long-term survey of the ACROSTUDY Spanish cohort, previously un- or partially responsive to surgery, radiotherapy or medical therapy, confirms that PEG is a very effective treatment to control acromegaly, with 67.9 % of IGF-I normalization at month 60 and 85.5 % of IGF-I control at any time throughout the course of treatment, despite the low doses used. However, this efficacy is lower than described in pivotal studies reflecting the usual difference between real-life practice and a clinical trial. Moreover, PEG has an excellent safety profile. The remaining challenge is to get a better dose titration, overcoming difficulties or fears about treatment safety and improving the outcomes of acromegalic patients.

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Compliance with ethical standards

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