Long-Term Efficacy and Safety of Pegvisomant in Combination With Long-Acting Somatostatin Analogs in Acromegaly

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Background: Treatment for acromegaly patients with long-acting somatotropin release-inhibiting factor (LA-SRIF) often does not result in complete normalization of IGF-1. Addition of pegvisomant (PEGV), a GH receptor antagonist, could improve this; however, the literature has not described long-term follow-up.

Objective: To assess long-term efficacy and safety of this combined treatment in the largest current single-center cohort of patients, from 2004–2013.

Design: Acromegaly patients were treated for at least 6 months with a high-dose LA-SRIF. To patients with persistently elevated IGF-1 levels ($>1.2 \times$ upper limit of normal) or poor quality of life, PEGV was added as one weekly injection.

Results: The patients (n = 141) were treated with PEGV and LA-SRIFs for a median period of 4.9 years (range, 0.5–9.2). Efficacy, defined as the lowest measured IGF-1 level during treatment, was 97.0%. The median PEGV dose to achieve this efficacy was 80 mg weekly (interquartile range, 60–120 mg). Combination treatment-related adverse events were recorded in 26 subjects (18.4%). Pituitary tumor size increase was observed in one patient. Injection-site reactions were observed in four subjects. In 19 patients (13.5%), transiently elevated liver transaminases of more than three times the upper limit of normal were observed, of which 83% occurred within the first year of combination treatment. Eight patients died, at a mean age of 71 years; none of them were considered treatment-related.

Conclusions: The combination treatment with LA-SRIFs and PEGV was effective in 97% of the patients, it appears to be a safe medical treatment and it reduces the required dose of PEGV. (***J Clin Endocrinol Metab*** **99: 3644–3652, 2014)**

Acromegaly is a rare disease that is almost exclusively caused by a GH-secreting pituitary tumor that results in signs and symptoms and reduced life expectancy (1). Treatment is focused on improving life expectancy, reducing signs and symptoms, and thereby increasing the patients' quality of life (QoL). These main objectives are considered to be accomplished when serum levels of IGF-1 and GH are normalized. This is achieved in less than 60%

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetes mellitus type 2; HPRT, hypoxanthine phosphoribosyltransferase; IQR, interquartile range; LA-SRIF, long-acting somatotropin release-inhibiting factor; MRI, magnetic resonance imaging; PEGV, pegvisomant; QoL, quality of life; SDS, SD score; SSTR, somatostatin receptor; TET, transient elevated transaminase; TSS, transsphenoidal surgery; ×ULN, times upper limit of normal.

of patients after surgery (2, 3). Normalization after medical treatment occurs in 30% to over 90% of patients (4–7). Current medical treatment modalities focus on the normalization of IGF-1 by targeting pituitary GH production or peripheral GH actions. In 1985, studies demonstrated that GH secretion by GH-secreting pituitary tumors could be inhibited by somatostatin analogs (8). Thereafter, many studies on the efficacy of long-acting somatostatin release-inhibiting factor (LA-SRIF) analogs to control pathological GH secretion reported an average normalization of IGF-1 and GH (<2.5 μg/L) in 44% of patients treated with LA-SRIFs (4).

More recently, pegvisomant (PEGV) was introduced (9). This drug is a genetically modified analog of human GH; because it binds to but does not activate the GH receptor, it acts as a competitive GH receptor antagonist (9). The first report on its long-term efficacy and safety was published early this century (10). PEGV was approved in Europe in 2002, followed by the United States in 2003. Although PEGV clinical trials found efficacy rates $>$ 90% (6, 9, 10), these were not confirmed by observational studies such as ACROSTUDY and the German Pegvisomant Observational Study (7, 11–13). Nevertheless, phase IV noninterventional studies such as ACROSTUDY are designed to gather additional medical information complementary to placebo-controlled, randomized clinical trials (7, 14), such as rare adverse events and atypical treatment reactions (15). Therefore, the ACROSTUDY is less suitable to assess efficacy. The adverse events reported during PEGV treatment seem relatively mild, the most frequent being transient elevated transaminases (TETs), followed by local lipohypertrophy at the injection site (6, 7, 16, 17).

In 2005, the first study on the combined treatment of acromegaly with weekly PEGV and LA-SRIFs reported high efficacy, as well as possible cost reductions due to the lower median PEGV dose needed (18). Thereafter, long-term data on efficacy and safety showed an efficacy rate of $>$ 90% and the possibility of lowering the necessary dose of PEGV when combined with LA-SRIFs (16, 17, 19). Combined treatment was also able to improve QoL in LA-SRIF-controlled patients (20).

Because PEGV competitively blocks the GH receptors in all peripheral tissues, it does not prevent tumor growth of the pituitary adenoma (6). In previous studies with LA-SRIFs and PEGV, tumor size increase was not observed, and in a significant number of patients (19%), the tumor size even decreased (16, 17). Although combination treatment and PEGV monotherapy appear to have similar efficacies (6, 7, 16), side effects such as TETs seem to occur more frequently during combination therapy (7). No studies could detect any factor that predicts elevations of the liver enzyme alanine aminotransferase (ALT), except one that reported that carriers of UGT1A1*28 polymorphism of Gilbert's syndrome seem to have a higher risk of developing PEGV-induced liver injury (21).

Combination therapy might be an attractive option for treating acromegaly, but the long-term effects outside of the clinical studies such as the ACROSTUDY remain uncertain.

Here we report on the long-term efficacy and safety of combined treatment with PEGV and high-dose LA-SRIF treatment for almost a decade in a single tertiary referral center.

Patients and Methods

Data were collected from all consecutive patients who were treated with LA-SRIF for at least 6 months (n = 141) at our Pituitary Center Rotterdam between 2004 and 2013. Permission from the Institutional Review Board of the Erasmus Medical Center Rotterdam was obtained for all the substudies involved, and all patients gave their written informed consent. All patients were initially started on LA-SRIF monotherapy in a stable dose, after which PEGV was added by a weekly injection.

Results were derived from two data sets. The first contains data from acromegaly patients (n = 112) with elevated IGF-1 levels ($>1.2 \times$ the upper limit of normal [$\times$ULN]), after at least 6 months of high-dose LA-SRIFs (Sandostatin LAR 30 mg or Lanreotide Autogel 120 mg every 28 d). This group is described in this article as the "uncontrolled group." Acromegaly patients in the second group (n = 29) were cotreated with PEGV to improve the QoL as add-on therapy on top of LA-SRIFs, which already had normalized their IGF-1 levels. They are designated as the "QoL group." In our analyses, this QoL group was only used for the assessment of safety aspects.

In the uncontrolled group, 27 acromegaly patients started with 25 mg PEGV weekly as cotreatment, whereas another 18 started with 40 mg PEGV weekly, and the last 67 patients started with a variable dose of PEGV weekly, guided by their baseline IGF-1. The variable starting dose was based on one of our previous reports (17) (see Figure 2). The formula to calculate the PEGV dose is: 4 + (IGF-1 z-score during treatment with high-dose LA-SRIF*16), which was derived from a method described previously (17). This formula can only be used when IGF-1 is elevated after a period of at least 6 months of LA-SRIF treatment.

Intervals of dose adaptations were 6–8 weeks, until a controlled IGF-1 level was achieved on two consecutive occasions. The subjects then visited our outpatient clinic every 16 weeks. For the QoL group, methods were described previously (16).

When the once-weekly PEGV dose exceeded 80 mg per injection, patients divided the dosage into two weekly injections. With weekly doses over 200 mg, subjects changed administration intervals into daily injections or five injections per week. At each visit to our outpatient clinic, efficacy and safety parameters were assessed.

The efficacy parameter IGF-1 was assessed using the Immulite 2000 assay (DPC Biermann GmbH/Siemens), a solid-phase, enzyme-labeled, chemiluminescent immunometric assay with an intra-assay variability of 2–5%, and an intra-assay variability of 3–7%. The IGF-1 age- and sex-adjusted reference ranges were

used from an article by Elmlinger et al (22). PEGV serum levels were assessed in Arhus, as described in a previous report (23).

Safety assessments included: electrocardiogram, serum concentrations of ALT, aspartate aminotransferase (AST), alkaline phosphatase, γ-glutamyl transpeptidase, total bilirubin, and lactate dehydrogenase. Magnetic resonance imaging (MRI) assessed changes in pituitary tumor volume at least annually. Decrease of tumor size was determined by one radiologist, who was blinded for the outcome. Decrease was defined as more than a 20% reduction of the largest diameter of the tumor during combination treatment compared with the largest diameter of the last MRI before the addition of PEGV.

Genomic DNA was isolated from peripheral blood leukocytes. A 324-bp fragment of the UGT1A1 gene promoter, which includes the TATA box, was PCR-amplified by using forward (5′-GAGTATGAAATTCCAGCCAG-3′) and reverse (5′-GGATCAACAGTATCTTCCC-3′) primers and platinum Taq Mix (Invitrogen). Cycle conditions were 95°C for 5 minutes, followed by 35 cycles of 95°C for 30 seconds, 60°C for 30 seconds, 72°C for 30 seconds, and 72°C for 7 minutes. The results were ascertained on the 3500 Genetic analyzer (Applied Biosystems). Gilbert's syndrome was characterized by an additional TA repeat in the TATA sequence of the UGT1A1 promoter region, ie, A(TA)7 TAA instead of A(TA)6 TAA. Results were first published by Bosma et al (24).

Somatostatin receptor type 2 (SSTR2) mRNA expression was performed in one patient's tumor sample, described in *Results*. Real-time quantitative PCR was performed as previously published (25). Sequences and concentrations of the SSTR2 primer-probe pairs and of the hypoxanthine phosphoribosyltransferase (HPRT) are described in the same previously published report (25). We used the ABI Prism 7900 Sequence Detection System (Applied Biosystems) to measure the samples and compared it with the housekeeping gene HPRT.

Statistical methods

Data are expressed as median (interquartile range [IQR]) unless otherwise specified. Differences between two or more independent subgroups were analyzed using the Mann-Whitney *U* test and the one-way ANOVA (multiple comparison), respectively. Paired data were analyzed with the Wilcoxon's signed-rank test. Nominal variables were analyzed using the χ^2 test. *P* values $< .05$ (two-tailed) are considered statistically significant. Statistical analyses were performed by SPSS version 20 (SPSS Inc) and GraphPad Prism version 6 for Windows (GraphPad Software, Inc).

Results

Efficacy

Patient characteristics are depicted in Table 1. The median duration of PEGV treatment was 4.9 years (range, 0.5–9.2). Normalization of IGF-1 for age and sex, defined as the lowest IGF-1 during treatment, was observed in 97.3% of the subjects. The absolute median IGF-1 level was 18.0 nmol/L (IQR, 13.4–23.6), 0.56×ULN of IGF-1 (IQR, 0.43–0.74), or expressed as SD score (SDS), −0.16 (IQR, −1.27 to 0.90). All patients had a lowest IGF-1 level below 1.2×ULN. The median weekly PEGV dose to achieve these lowest IGF-1 levels was 80 mg (IQR, 60–120 mg). The IGF-1 level at the last visit was 26.0 nmol/L (IQR, 20.0–34.4), 0.85×ULN (IQR, 0.67–1.09), or expressed as SDS 1.50 (IQR, 0.49- 2.84). The median necessary dose of PEGV to achieve this IGF-1 level was 80 mg weekly (IQR, 60–130). There was no significant difference between the PEGV dose during the lowest IGF-1 and the PEGV dose at the last visit ($P = .106$).

Table 1. Patient Characteristics

Sex, % males	58.0
Age, y	48.2 (39.0–59.1)
Tumor volume, % macro	81.3
Diabetes mellitus, %	36.9
Gilbert's polymorphism, %	
Heterozygous	43.1
Homozygous	11.5
Previous therapy, %	
Surgery	30.4
Radiotherapy	0.9
Surgery and radiotherapy	10.7
IGF-1 at start of PEGV, nmol/L	66.5 (46.4–87.9)
IGF-1 ×ULN at start of PEGV	1.89 (1.48–2.56)
IGF-1 expressed as SDS at start of PEGV	8.02 (5.10–11.13)

Data are expressed as median (IQR) or percentage.

The weighted median control of IGF-1 levels (1.2×ULN) over years 1 to 9 was 89.7%, with a median PEGV dose of 73.8 mg weekly. The median control of IGF-1 (1.0×ULN) over years 1 to 9 was 78.0%. The annual results from years 1 to 9 of the median IGF-1 and PEGV levels are depicted in Figure 1. In Supplemental Figure 1, the normalization rate during the first year and the necessary PEGV dose are depicted. A clinical tool is depicted in Supplemental Figure 2. This figure shows the required dose of PEGV that is necessary to normalize the IGF-1 level.

Normalization rate, expressed as the lowest IGF-1 level, was not significantly different between patients with (95.0%) or without (98.6%) diabetes mellitus type 2 (DM) ($P = .588$). The necessary dose to achieve this was identical for non-DM and DM ($P = .281$). Normalization of IGF-1 levels was achieved in 95.7% of patients who had undergone prior pituitary surgery, which was comparable to the outcome in patients receiving primary medical treatment (98.5%; $P = .604$) and with no difference between the two groups in the PEGV dose ($P = .518$). This was also the case when radiotherapy was excluded from the analysis ($P = .901$).

No significant differences in normalization rate and PEGV dose necessary to control IGF-1 were observed between genders ($P = .997$, $P = .225$, respectively), microadenomas vs macroadenomas ($P = .711$, $P = .809$, respec-

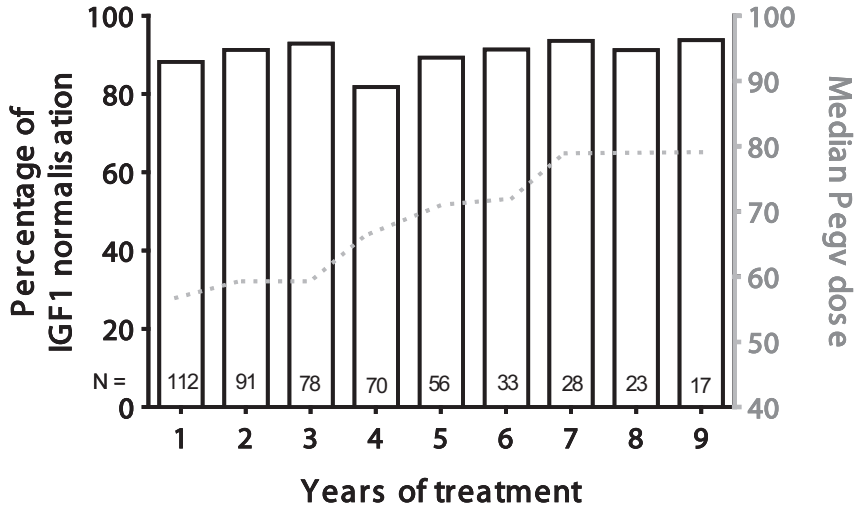

Figure 1. IGF-1 serum levels < 1.2×ULN years 1–9. Percentages of patients with IGF-1 < 1.2×ULN (left axis) and median PEGV doses (dotted line right axis) are shown for every individual year during the 9 years of treatment. Cumulative numbers of the included patients at each treatment year are depicted at the bottom of every bar. All patients (n = 112) were treated for at least 1 year, 17 patients were treated for the maximal 9 years of follow-up.

tively), or carriers vs noncarriers of Gilbert's polymorphism ($P = 1.000$, $P = .789$, respectively).

In 11 patients, surgery was performed during combination therapy. In Supplemental Table 1, the reasons for surgery are depicted. The PEGV dose before operation was 120 mg (IQR, 80–160 mg). One patient was cured after transsphenoidal surgery (TSS). Six patients could discontinue PEGV and continued with a high dose of LA-SRIFs after significant tumor debulking. The other five patients continued with 80 mg (IQR, 80–100 mg) PEGV weekly.

Safety

Liver tests

ALT and AST were normal at baseline in all patients. TETs of more than 3×ULN were observed in 22 patients (15.6%; Table 2). All cases were transient without adaptation of PEGV dose or discontinuation, except for one patient with TET 26.1×ULN, who was previously reported (26) and developed a second period of TET > 2×ULN after re-exposure to PEGV monotherapy. The development of TET was not influenced by the PEGV dose ($P = .803$). Obstruction of the biliary tract could be an explanation for three of these cases, so in 19 patients

Table 2. TET Patients During PEGV Treatment of Acromegaly

Patient no.	Sex	PEGV Dose During TET, mg/wk	Peak TET (×ULN)					DM	Gilbert's Polymorphism	Clinical Features
			Bili	Alk Phos	γ-GT	AST	ALT			
1	M	30	0.7	0.6	2	4.0	4.7	−	Normal	
2	M	300		1.0	1.8	5.0	5.5	−	Normal	
3	M	40	0.4	1.2	0.9	4.3	7.0	−	Normal	
4	M	160	0.4	1.2	1.8	4.6	6.5	+	Normal	
5	M	80	1.1	0.5	2	3.5	3.9	−	Heterozygous	
6	M	60	2.3	2.9	16.7	16.7	25.8	+	Homozygous	MRCP: cholecystolithiasis
7	M	60	0.6	0.8	1.8	2.4	3.6	−	Heterozygous	
8	M	40	5.3	0.9	5.1	4.9	8.0	−	Homozygous	Ultrasound: cholecystolithiasis
9	M	80		0.9	0.8	3.1	1.2	+	Heterozygous	
10	M	40	1.6	1.1	4.6	3.1	4.3	−	ND	
11	M	40	2.0	1.4	8.8	9.5	8.3	−	Homozygous	
12	M	60	0.9	1.2	4.8	6.3	13.2	−	Normal	
13	M	80	1.3	2.6	11.8	5.6	3.7	−	Heterozygous	Ultrasound: cholecystolithiasis
14	M	60	1.3	1.3	6.9	13.7	26.1	+	Heterozygous	
15	F	80	0.8	0.8	1.5	2.9	4.5	+	Normal	
16	F	20	1.0	0.6	0.9	7.5	10.0	−	Heterozygous	
17	F	60	0.7	0.7	2.7	2.8	4.0	−	Heterozygous	
18	F	60			3.9	–	4.6	−	Homozygous	
19	F	160		1.1	4.1	2.4	3.7	−	Normal	
20	F	20		0.9	2.3	2.8	3.7	+	Normal	
21	F	40	1.3	0.7	1.3	8.4	11.7	−	Normal	
22	F	60		1.0	1.5	4.0	4.8	−	Heterozygous	
Second period of TET										
16	F	40		0.5	0.5	6.1	7.1	−	Heterozygous	
20	F	60		2.0	9.9	2.4	4.0	+	Normal	

Abbreviations: M, male; F, female; Bili, total bilirubin; Alk Phos, alkaline phosphatase; γ-GT, γ-glutamyl transpeptidase; ND, not determined; MRCP, magnetic resonance cholangiopancreatography.

(13.5%) TET could be linked to PEGV treatment. Reexposure to PEGV after discontinuation resulted in a second period of TET > 3×ULN in two patients during combination therapy. TET > 3×ULN occurred after a median period of 5.2 months (IQR, 3.2–13.3) (see Supplemental Figure 3). In a median period of 5.5 months (IQR, 3.0–14.0), TET normalized again (see Supplemental Figure 4).

Gilbert's polymorphism

Gilbert's polymorphism (UGT1A1*28) was assessed in 131 (93%) of the 141 patients. No blood could be obtained from 10 patients. UGT1A1*28 was observed in 71 (54.2%) patients, 11.5% homozygous and 42.7% heterozygous. Of the 22 TET cases, four (18.2%) were homozygous, and eight (36.4%) were heterozygous. No association between UGT1A1*28 and TET was found in patients with heterozygous ($P = 1.000$) or homozygous polymorphism ($P = .827$). The same lack of association applied to heterozygous UGT1A1*28 compared to homozygous ($P = .752$). Neither sex ($P = .393$) nor DM ($P = .956$) was associated with TET.

Pituitary tumor size

Decrease in tumor size, defined as a decrease of more than 20% during combination treatment, was observed in 13 patients (16.9%), whereas size could not be determined in patients with the presence of an empty sella (n = 8) or in whom radiotherapy was performed (n = 13). During combined treatment, pituitary apoplexy occurred in two patients without a necessity for surgical intervention. In one patient, surgery was needed due to true tumor size increase. This case is described at the end of the *Results, Two exceptional patients (tumor growth)*.

Injection-site reactions

Injection-site reactions were observed in four subjects (2.8%). In three patients, lipohypertrophy appeared to be reversible by a more frequent rotation of the injection site. Nevertheless, one of these patients decided for TSS (see Supplemental Table 1) in order to be able to stop PEGV treatment. After TSS, the patient was able to stop the PEGV and to lower the LA-SRIF dose. One patient underwent cosmetic surgery due to lipohypertrophy.

Mortality

During the 9 years of follow-up, eight patients died (5.6%). All deaths were considered to be unrelated to the treatment. In Supplemental Table 2, the causes of death are listed. The average age of the patients who died was 71 years (range, 51–86). All patients had significant comorbidities such as cardiovascular, cerebrovascular, malignant, or pulmonary disease.

Supplemental Table 3 shows an overview of patients published before by our research group.

Two exceptional patients

Tumor growth

The first patient, a 25-year-old female, showed significant tumor growth during the combination therapy. In 2011, the patient presented with bitemporal hemianopia; therefore, TSS was performed. Retrospectively, her symptoms were presented 2 years before the diagnosis. Before surgery, IGF-1 was 127 nmol/L (2.9×ULN). After surgery, the bitemporal hemianopia resolved, and other pituitary axes remained unaffected. Octreotide LAR 20 mg monthly was started, and the IGF-1 level dropped to 67 nmol/L (1.6×ULN) 5 months after surgery. Octreotide LAR was increased to 30 mg every 3 weeks because IGF-1 was still elevated. Despite the change in dose, the IGF-1 level rose to 100 nmol/L (2.3×ULN). Pituitary MRIs (Figure 2, A–C) performed 3 and 8 months after surgery showed a large tumor remnant. After 11 months, the LA-SRIF IGF-1 level was 87 nmol/L (2.0×ULN), and GH was 105 μg/L; at this stage, the patient was transferred to our hospital. IGF-1 normalized with Sandostatin LAR 30 mg and PEGV 80 mg twice weekly. Seven months after the addition of PEGV, an increase in tumor size was observed (Figure 2D) and a second TSS was needed, which was followed by radiotherapy. PEGV was restarted after surgery in combination with Sandostatin LAR 30 mg. A weekly dose of 100 mg of PEGV normalized the IGF-1 level. To date, IGF-1 remains normal, and the tumor size is stable. The pathology report after the first surgery revealed a GH-secreting adenoma with a Ki-67 index of 1%. After the second surgery, the pathology reported sparsely granulated GH-secreting adenoma with a Ki-67 index of 1–2%; additionally, receptor expression was determined on the tumor specimen (Figure 3A). SSTR2 mRNA expression could be demonstrated (0.3; expressed as relative expression of HPRT), as well as SSTR1 and SSTR5 mRNA expression. Incubation of primary cultures of dispersed somatotroph tumor cells of this patient with octreotide resulted in significant reduction of GH secretion (15.5%; $P < .01$; Figure 3B).

Increasing demand for PEGV

The second patient, a 29-year-old male, started combination therapy in 2007 after TSS and transfrontal surgery. Normalization of IGF-1 was achieved after 9 months with a PEGV dose of 210 mg weekly (Figure 4). Eight months after normalization, the IGF-1 increased again

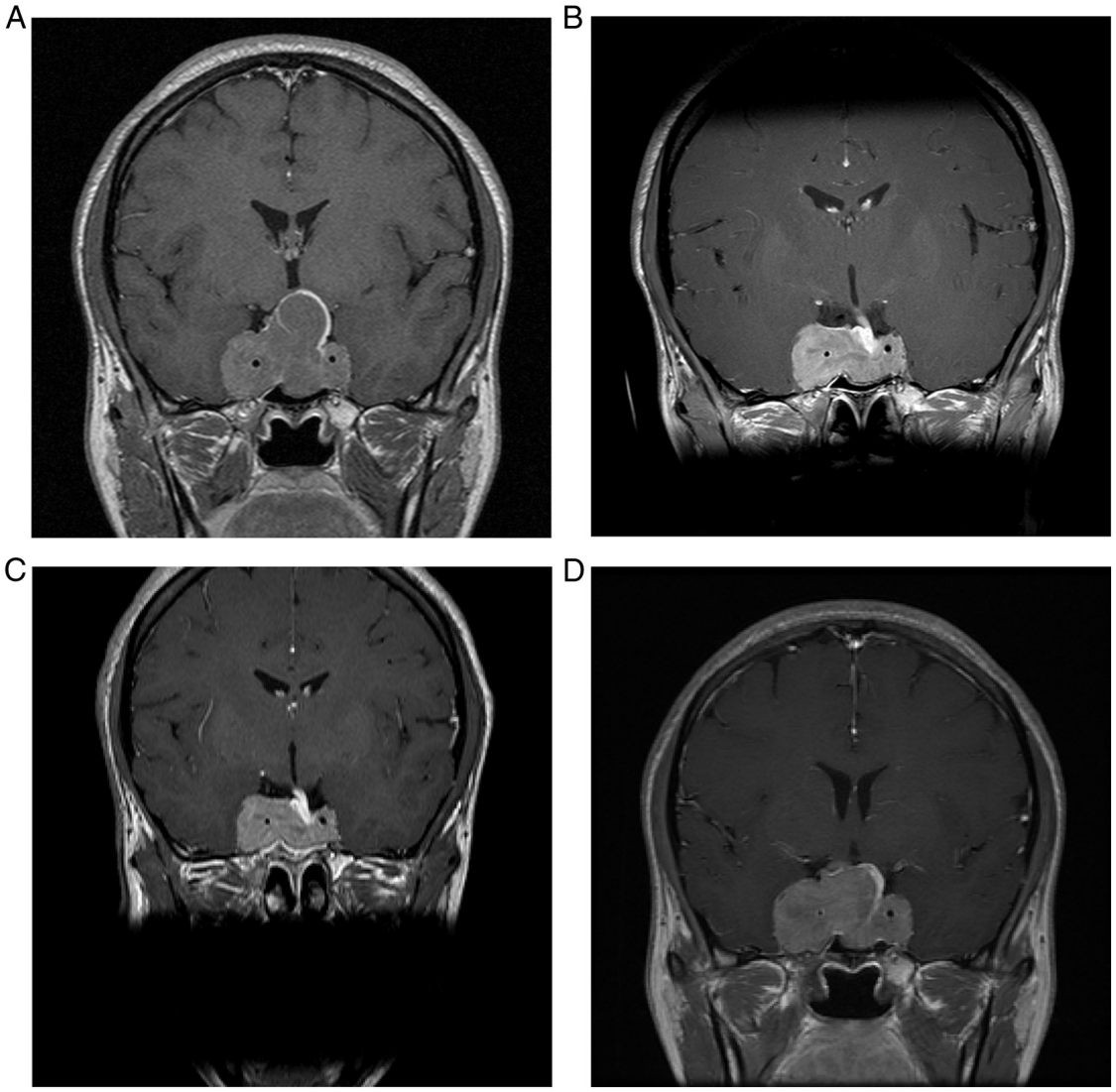

Figure 2. Magnetic resonance images of first patient (tumor growth). A, At diagnosis. B, Three months after the first surgery, no medical treatment. C, Eight months after the first surgery, Sandostatin LAR 20 mg every 4 weeks. D, Seven months after the addition of PEGV, Sandostatin LAR 30 mg every 4 weeks + PEGV 160 mg weekly.

above the ULN. In the subsequent 3 years (2008–2010), the IGF-1 level continued to increase despite a stepwise doubling of the PEGV dose to 420 mg weekly. PEGV was still given in combination with a high-dose LA-SRIF (Lanreotide Autogel, 120 mg every 3 wk). At the end of 2010, the combination therapy was sufficient to decrease the IGF-1 below the ULN for 2 years, but the IGF-1 level rose again in 2012. During these periods of IGF-1 increase, additional MRIs were assessed but did not show any tumor size increase. PEGV injections were supervised at the hospital on several occasions in order to check the administration procedures and compliance. Retrospectively, PEGV levels were measured (Figure 4). GH levels did not increase significantly, and no PEGV antibodies were detected. Serum PEGV level in relation to injected doses and IGF-1 levels are depicted in Figure 4.

Discussion

Combined treatment has a high efficacy, similar to the clinical registration trials, and seems to be safe. Almost all of the adverse events occurred within the first year and were transient.

The efficacy and safety of the combination therapy that we report here are based on data that we obtained from a single tertiary referral center. All patients attended the outpatient clinic on a regular basis and under the supervision of experienced pituitary endocrinologists. This approach could explain the superior outcome as compared to the results reported in the ACROSTUDY, which contains patients treated at centers with less experience. Recent reports suggest that the efficacy of PEGV treatment (7, 13) is not as high as reported by the clinical trials using mono-

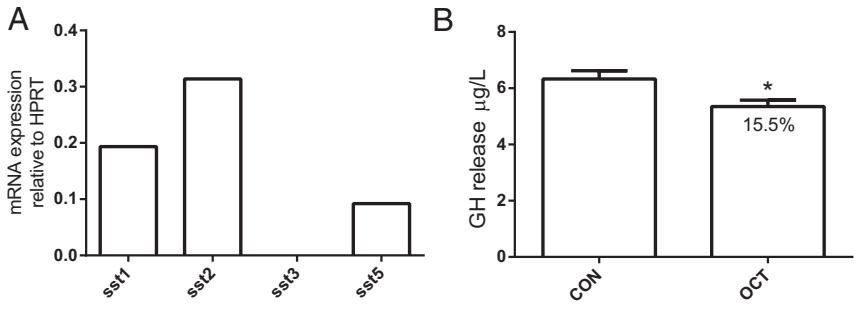

Figure 3. Tumoral mRNA receptor expression. A, In vitro function tests. Tumoral SSTR2 mRNA expression is 0.3, expressed as relative to the expression of HPRT. Sst, somatostatin receptor. B, Incubated primary cultures of dispersed somatotroph tumor cells with octreotide. Tumor cells were available after TSS because of tumor growth in a patient during combination therapy. Shown here is a significant decrease of GH secretion by 15.5%. CON, control; OCT, octreotide 10 nM. *, $P < .001$.

therapy of PEGV (9, 10). Our data, however, show that PEGV in combination with LA-SRIF is as effective as in clinical trials, provided that optimal dosing is applied.

In our opinion, rare diseases should be treated in dedicated expert centers only. This has been clearly shown for neurosurgery in acromegaly (27). Therefore, it would make sense that medication indicated for the treatment of acromegaly is restricted to specialized centers. The large number of PEGV-treated acromegaly patients in our center has brought about more experience and a more structural approach, which might explain in part the higher efficacy that we achieved compared to more recent literature (7). However, dosing strategies could be suboptimal, even in highly experienced centers, due to local legislation or reimbursement issues.

Studies in the field have used different criteria for the assessment of IGF-1 levels. Some use the lowest IGF-1 and end-of-study IGF-1, and others the lowest annual IGF-1. The current data underline the fact that efficacy numbers are a matter of definition. The cotreatment study of PEGV with Lanreotide Autogel used end-of-study and lowest IGF-1, and efficacy was 58 and 79%, respectively (28). The initial registration studies (10) and our combined treatment study (6) used the lowest IGF-1, and the efficacy rates were over 90%. With the current data set, a similar efficacy of 97.3% is observed, assessing lowest IGF-1 recorded during treatment in a specialized center with standardized methods and not from a clinical trial with irregular follow-up.

Surgery before combined treatment did not significantly reduce the required dose of PEGV to normalize IGF-1. This is in line with our previous observations (6, 16, 17). In the current study, 11 patients underwent surgery during combined treatment. In five patients, the pre- and post-surgery PEGV doses were more or less similar. The decision to perform surgery in such cases therefore remains difficult.

The incidence of TETs and local effects of PEGV at the injection site have been previously reported by several groups (7, 10, 11, 13, 17, 29, 30). The incidence of TET during combination therapy seems to be higher compared to PEGV monotherapy. Reported incidences during combination therapy range from 11–15% when an ALT cutoff of 2×ULN or 3×ULN is used (16, 28). During PEGV monotherapy, an incidence of elevated transaminases was reported to be 5.2% (13). In the ACROSTUDY, only 30 patients (2.5%) had an AST or ALT above 3×ULN (7). Most of the patients with TET were on combination treatment (7). However, the real frequency of PEGV-related TET during monotherapy in this cohort might be underestimated. Elevated transaminases are usually transient, patients are usually not seen in a systematic, repetitive way, and therefore TET will go unnoticed. This can explain part of the difference in TET between our 15% and the 2.5% in the ACROSTUDY. Our data support the notion that TET seems to occur more frequently during combined treatment. We recommend careful monitoring of patients with TET > 3×ULN. Cholelithiasis must be excluded by an ultrasound of the liver. In patients with TET > 10×ULN, we also recommend doing a liver biopsy and discontinuing PEGV in case of drug-induced hepatitis.

We found an association between DM and TET in 2007 (17), but it was not found in a more recent study (16) or in the current evaluation of the long-term treatment data. A few years later, a Spanish group observed

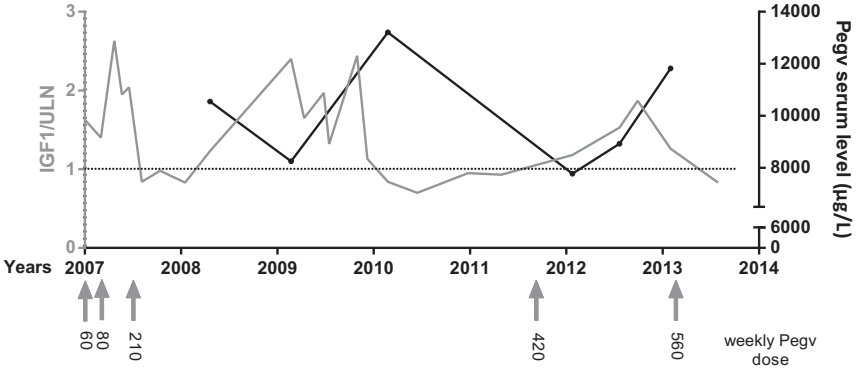

Figure 4. IGF-1 serum level and PEGV serum level during time. IGF-1 serum levels expressed as ULN (gray line) and PEGV serum levels (µg/L, black line) of one patient during years of combination treatment. The arrows show the moment of PEGV dose increase (mg/wk).

an association between a common polymorphism (UGT1A1) of Gilbert's syndrome and male sex and TET (21). In our large single-center cohort, we detected this polymorphism in 54.2% of our patients. However, we could not find a dose effect between wild-type and homo- or heterozygous carriers of this polymorphism of Gilbert's syndrome. Moreover, we could not confirm any association with TET and the polymorphism. No other association for TET could be observed in this database. Therefore, there is still no explanation for the TET during PEGV treatment, except for the hypothesis that combined LA-SRIF and PEGV increases the intrahepatic lipid content assessed by MRI that could lead to TET (31).

From the current data, it is clear that combined treatment usually stabilizes or decreases pituitary tumor size, which is in line with our previous observations (16). In some patients, tumor size decrease was observed; however, in one patient tumor size was increased. This was an exceptional patient with a short duration of symptoms before diagnosis and a significant SSTR2 expression, but only an octreotide-mediated GH decrease in vitro of 15.5%. In most GH-adenoma cultures with similar SSTR2 expression, GH secretion decreases 50% or more after treatment with a similar dose of octreotide (32). Therefore, it is likely that a postreceptor defect was present in this tumor, explaining the lack of biochemical control during LA-SRIF alone and tumor size control during combined treatment.

During long-term control of IGF-1 with combination therapy, PEGV dose does not increase. In one exceptional case, dose adaptation was needed to treat the escape in IGF-1 levels over time, without any change in tumor volume. PEGV injection instruction was repeated several times, as was supervised injection. We could not observe any aberrant injection pattern at any of these supervised moments. The single Dutch pharmacist who provides PEGV throughout The Netherlands was asked to review the amount of delivered PEGV. The pharmacist could not find any disparity between the amount of PEGV delivered to the patient and the amount prescribed.

Certain studies report large interindividual differences in PEGV serum levels with similar PEGV dose administrations (23, 33); however, there are only limited data on serum PEGV levels during long-term use. The patient from our series who needed a very high PEGV dose to obtain disease control also exhibited very high serum PEGV levels, suggesting adequate compliance and no obvious evidence of increased clearance of the drug.

Conclusion

Combined treatment for acromegaly for almost a decade appears highly effective and comparable to the original registration trials, providing that the proper PEGV dose is used. Side effects were mild and transient, and we could not confirm Gilbert's polymorphism as a cause of the observed transient elevated liver enzymes. Tumor size decrease was observed in 16.9% of the patients. However, one patient had continued growth of the pituitary adenoma despite normalization of IGF-1. The only way to identify these patients is continued, periodic monitoring by radiological imaging

We found that in combination with high-dose LA-SRIFs, the median dose of PEGV necessary to normalize IGF-1 levels (80 mg weekly) was considerably less than the dose of PEGV in those patients in the ACROSTUDY who did not normalize their IGF-1 during long-term treatment with PEGV only (140 mg weekly). This suggests that, for a significant number of patients, the combination of PEGV and LA-SRIFs is considerably less expensive. However, in one patient, dose increments of PEGV were required over time.

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