CLINICAL STUDY

Treatment of acromegaly with the GH receptor antagonist pegvisomant in clinical practice: Safety and efficacy evaluation from the German Pegvisomant Observational Study

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Abstract

Objective: The GH receptor antagonist pegvisomant is a highly effective new treatment option in acromegaly. The German Pegvisomant Observational Study (GPOS) was started to monitor long-term safety and efficacy of pegvisomant as prescribed in clinical practice.

Design: GPOS is an observational, multi-center, surveillance study, which comprises non-interventional data collection.

Methods: Of the 229 patients included in the study, 90.4% had previous pituitary surgery, 43.2% were treated by radiation therapy, and 94.3% had previous medical therapy for acromegaly that had been discontinued mainly due to persistent IGF-I elevation or side effects. The intention-to-treat population included 177 patients with at least one post-baseline efficacy measurement.

Results: IGF-I levels decreased from 1.75 ± 0.91 -fold the upper limit of normal at baseline to 1.05 ± 0.62 at the 6-month visit, 0.96 ± 0.60 at the 12-month visit, and to 0.89 ± 0.41 -fold after 24 months ($P < 0.0001$). Mean duration of pegvisomant therapy was 51.8 ± 35.8 weeks (median = 51.9 weeks). IGF-I was normalized in 64.4% at 6 months with a median dose of 15.0 mg/day, in 70.9% at 12 months, and in 76.3% at 24 months. Fasting glucose levels improved from 114.4 ± 45.9 to 101.5 ± 42.8 mg/dl after 6 months ($P < 0.01$) and to 100.6 ± 33.2 mg/ml after 12 months ($P < 0.01$). General physical condition measured by specific signs and symptoms score improved significantly. Adverse events occurring in $> 1\%$ were injection site reactions in 7.4%, elevated liver enzymes (> 3 times of normal) in 5.2% (3.1% spontaneously normalized during continued treatment), reported increase of pituitary tumor volume in 5.2% (which was verified in 3.1%), and headache in 1.7%.

Conclusions: Pegvisomant is generally well tolerated with a safety profile similar to that reported in clinical trials and can effectively reduce IGF-I in patients with acromegaly refractory to conventional therapy.

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Introduction

Acromegaly is a chronic endocrine disease characterized by excessive growth hormone secretion and consequently elevated insulin-like growth factor-I (IGF-I) levels, occurring in $> 95\%$ of the cases as a result of a benign pituitary adenoma. With reversing signs and symptoms of the disease as the main goal of therapy, transsphenoidal surgical intervention remains the treatment of choice. Medical therapy with dopamine agonists or somatostatin analogs is an adjunctive treatment option in case of inadequate disease control (1, 2). Recently, pegvisomant (Somavert), a pegylated recombinant analog of human growth hormone (GH)

which acts functionally as a GH receptor antagonist, received approval for the treatment of acromegaly (3–5). Data from clinical studies on the treatment of acromegaly have shown that the pegvisomant is a highly effective and well-tolerated therapeutic option for disease control with a normalization rate of IGF-I of up to 97% (6–9). Long-term data have so far been reported in only 152 patients who received pegvisomant by daily s.c. injection for up to 18 months (7). However, approximately 2000 patients have meanwhile received commercial drugs. Due to the limited long-term experience with the drug at the time of approval, the German Pegvisomant Observational Study (GPOS) was initiated in January 2004, immediately after the market

On behalf of the German Pegvisomant Investigators.

authorization of pegvisomant in Germany. The main goals of this non-interventional, observational study are the documentation and evaluation of long-term safety and efficacy of pegvisomant as prescribed under field conditions in clinical practice, i.e. if all decisions about pegvisomant treatment like switching from other treatments to pegvisomant, dose adaptation, or follow-up examinations are at the discretion of the responsible physician and are not given in the study protocol.

Here we report the safety and efficacy data from the first 229 patients who have been included in GPOS during the initial 2 years between January 2004 and December 2005.

Subjects and methods

GPOS

GPOS was started in January 2004 to monitor safety and efficacy of pegvisomant immediately after its market authorization in Germany in December 2003. GPOS uses a protocol that is similar to the protocol of ACROSTUDY, the Pfizer international database on pegvisomant treatment in acromegaly. It is an observational, multicenter, surveillance study, which comprises non-interventional data collection in accordance with the standard management of patients with acromegaly in everyday practice and in accordance with the recommendations of the pegvisomant (Somavert, Pfizer Pharma GmbH, Karlsruhe, Germany) summary of product characteristics. Indication for pegvisomant treatment and treatment monitoring were at the discretion of the responsible physicians' decision, i.e. no additional diagnostic or monitoring procedures were applied. Documented visits in the observational study are 6 and 12 months after the start of pegvisomant, and visits in yearly intervals thereafter. The study has been approved by the Independent Ethics Committee of the Charité Hospital, University of Berlin, Germany, and all patients have given their written informed consent.

Subjects

Between January 2004 and December 20th 2005, 229 patients (118 men, 111 women, age 49.5 ± 13.7 years, mean $\pm$ s.d.) were enrolled pro- and retrospectively in the study. Three patients were <18 years of age at baseline (15, 15, and 16 years). The patients have been treated in 77 centers all over Germany. The participating centers were departments of university hospitals ($n=41$), non-university hospitals ($n=13$), and field-based endocrinologists ($n=23$). Eight out of 77 participating sites have included more than seven patients, 47 sites have included between two and seven patients, and the other 22 sites have included only one patient each.

Methods

Serum IGF-I. Serum IGF-I levels have been measured in the local laboratories and interpreted according to the local, age-dependent reference ranges. Results were given as total IGF-I levels, and, to have a better comparability, as x -fold of the individual upper limit of normal (ULN). The methods used for IGF-I measurement were Nichols Advantage (Nichols Institute Diagnostics, Bad Vilbel, Germany), RIA-CT (Mediagnost, Reutlingen, Germany), the Immulite 2000 (DPC Biermann, Bad Nauheim, Germany), and the DSL ELISA or IRMA (Diagnostic Systems Laboratories, Sinsheim, Germany). In 52% of patients, IGF-I measurements were performed by the Nichols Advantage chemiluminescence assay, and were evaluated according to the published reference data by Brabant *et al.* (10).

Patient-assessed acromegaly symptom questionnaire (PASQ). The patients' symptoms were evaluated by completion of a questionnaire as used in the pivotal study on pegvisomant treatment (6). It is designed to evaluate the following symptoms and signs of acromegaly: headache, excessive sweating, joint pain, fatigue, soft-tissue swelling, numbness or tingling of limbs, and general physical condition. The answers were scored ranging from 0 (no symptoms) to 8 (severe, incapacitating symptoms) or 0 (best possible) to 10 (worst). In addition, a total score was calculated by adding the scores of all symptoms.

Statistical analysis. The statistical analysis was descriptive and exploratory. The efficacy analysis was performed in the intention-to-treat population (ITT). ITT was defined as all patients who received at least one dose of Somavert and who had baseline and at least one post-baseline efficacy measurement. One hundred and seventy-seven patients have been included in the ITT set. Data from the 12- and 24-month follow-up visits were available from 128 and 61 patients respectively. Change to the baseline of laboratory values and PASQ was tested with the two-tailed paired *t*-test at the 5% significance level. The safety analysis was performed in all 229 patients who had received at least one dose of pegvisomant (safety population), i.e. this population in contrast with the ITT population includes also patients with a recent start of pegvisomant who have not yet completed the 6-month visit. According to the protocol, physicians had to report all adverse events experienced by study patients regardless of their suspected causal relationship to pegvisomant and had to pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it met the criteria for classification as a serious adverse

event. In addition, the physician was required to assess causality and indicate that assessment.

Results

Baseline characteristics

The 229 patients documented (safety population) had an average 9.1 years history of acromegaly with a mean age at diagnosis of 40.5 ± 12.7 years. All but three patients had acromegaly due to a GH-secreting pituitary adenoma. In three patients, autonomous GH hypersecretion was documented clinically and biochemically without morphological evidence for a pituitary tumor by magnetic resonance imaging (MRI). Two patients had multiple endocrine neoplasia type I (both females, 15 and 60 years old at baseline, macroadenoma) and one patient had McCune Albright Syndrome (male, 15 years old at baseline). The size of pituitary tumor or residual adenoma at baseline before pegvisomant treatment was classified as macroadenoma in 92 out of 229 patients (40.2%) and as microadenoma in 56 patients (24.5%). Sixty-two patients (27.1%) had no visible tumor, 13 patients (5.7%) had a visible tumor without data on tumor size, and in six patients (2.6%), no data about baseline pituitary imaging were available.

Deficiencies of other pituitary hormones were documented at baseline before the start of pegvisomant in 41.2% for luteinizing hormone/ follicle-stimulating hormone, 38.9% for thyroid-stimulating hormone, and 34.1% for adrenocorticotrophic hormone. At the time of inclusion into GPOS, hyperprolactinemia was found in 14.1%, and 5.3% had diabetes insipidus.

Previous treatment of acromegaly

Of the safety population ($n=229$), 207 patients (90.4%) had previous pituitary surgery, 99 patients had previous radiation therapy (43.2%), and 216 patients (94.3%) had previous medical therapy for acromegaly. One hundred and ten patients (48.1%) had received dopamine agonists with some of them having been treated with several different drugs (bromocriptine in 57, cabergoline in 57, and quinagolide in 11 patients respectively). Two hundred and four patients (89.1%) had previously received octreotide, and 23 (10.0%) had received lanreotide. Twenty-one patients (9.2%) had already been treated with pegvisomant within clinical studies for a mean period of 6.7 months (median = 7.1 months) before inclusion in the GPOS. In 13 patients (5.7%), no previous medical treatment of acromegaly was documented. In the majority of patients, the reasons for discontinuation of treatment with somatostatin analogs and/or dopamine agonists were persistent IGF-I elevation and/or side effects of the previous medical treatment. Details about previous octreotide treatment are given in Table 1.

Table 1 Reasons for discontinuation of octreotide pretreatment in patients included in German Pegvisomant Observational Study (safety, $n=229$).

Patients pretreated with octreotide	204 (89.1%)	
Treatment duration (median)	26.3 Months	
Reasons for discontinuation ^a	n	%
Non-controlled IGF-I	139	72.0
Treatment complications	23	11.9
Non-controlled IGF-I and complications	12	6.2
Other	19	9.8

IGF-I, insulin-like growth factor-I. ^aData are available from 193 patients.

Concomitant diseases at baseline

At baseline, a high prevalence of concomitant diseases was reported in the overall cohort of patients ($n=229$). The most relevant disorders were gallstone disease in 24.4%, diabetes mellitus in 28.9%, heart failure (NYHA I–III) in 10.0%, cardiac arrhythmia in 7.9%, colorectal polyps or tumors in 17.2% (with only one case of colorectal cancer), breast cancer in 3.6% of the female patients, and prostate cancer in 5.1% of the male patients.

Treatment with pegvisomant

The mean dose of pegvisomant in the safety population ($n=229$) at the time of interim analysis was $16.5 \text{ mg/days} \pm 7.7$ with 94.1% of patients receiving pegvisomant doses between 10 and 30 mg/days. Five patients had 10 mg pegvisomant every second day, two patients received 35 mg/days, three patients received 40 mg/days, and one patient received 50 mg/days. At the time of closing data, 177 patients had completed the first follow-up visit after a mean interval of 6.2 months from start of pegvisomant treatment. A second follow-up after 12.9 months has been completed by 128 patients, and a third follow-up after 23.8 months from baseline by 61 patients. Out of 121 patients who have reached normal IGF-I levels on pegvisomant treatment and who have information available about the pegvisomant dose from at least one additional follow-up visit, 54 (44.6%) remained at the same pegvisomant dose during follow-up, in 59 patients (48.8%) the pegvisomant dose was increased and in eight patients (6.6%), the dose could be reduced. Body weight did not significantly change during pegvisomant treatment (baseline, $89.9 \pm 19.7 \text{ kg}$; after 6 months, $89.8 \pm 17.7 \text{ kg}$; after 12 months, $90.8 \pm 17.8 \text{ kg}$; and after 24 months, $89.4 \pm 15.8 \text{ kg}$).

Course of IGF-I during treatment with pegvisomant

The course of IGF-I during treatment has been evaluated in the ITT population ($n=177$). Locally measured baseline IGF-I levels were available before start of pegvisomant in 150 patients and have been evaluated

for the follow-up within 6 months up to 2 years. During follow-up, locally measured IGF-I was available in 147 (6 months), 102 (12 months), and 39 (24 months) patients of the ITT population. In these patients, absolute IGF-I levels decreased from 526 ± 232 $\mu\text{g/l}$ at baseline to 303 ± 170 $\mu\text{g/l}$ at the 6-month visit, 276 ± 146 $\mu\text{g/l}$ at the 12-month visit, and 288 ± 176 $\mu\text{g/l}$ at the 24-month visit. When expressed in relation to the individual reference ranges, IGF-I levels decreased from 1.75 ± 0.91 -fold ULN at baseline to 1.05 ± 0.62 at the 6-month visit, 0.96 ± 0.60 at the 12-month visit, and to 0.89 ± 0.41 -fold ULN after 24 months (Fig. 1). At baseline, 24 patients had normal IGF-I levels (11.9%). After 6 months, IGF-I levels within the normal range were found in 64.4% of patients, in 70.9% after 12 months, and in 76.3% after 24 months. When comparing pegvisomant doses in the group of patients with normalized IGF-I at the 12-month visit ($n=89$) and in the group with non-normalized IGF-I ($n=35$), higher doses were used in the non-normalized group (20.7 mg/days ± 8.8 vs 18.2 mg/days ± 8.1 , $P=\text{ns}$). However, despite not normalized IGF-I, 42.8% of these 35 patients were treated with either 10 or 15 mg pegvisomant/days indicating that dose adaptation was not yet finalized (Fig. 2).

Glucose metabolism

In the ITT population, fasting glucose levels improved significantly from 114.4 ± 45.9 mg/dl ($n=114$) to 101.5 ± 42.8 mg/dl ($n=98$) after 6 months ($P<0.01$,

Figure 1 Course of insulin-like growth factor-I (IGF-I) during treatment with pegvisomant in the intent-to-treat population ($n=177$). IGF-I levels are expressed as x-fold the upper limit of normal (ULN; mean $\pm$ s.d.). At baseline $n=150$, after 6 months $n=147$, after 12 months $n=102$, and after 24 months $n=39$. * $P<0.0001$ vs baseline.

t -test, exploratory), to 100.6 ± 33.2 mg/dl ($n=65$) after 12 months ($P<0.01$), and to 96.5 ± 18.8 mg/dl ($n=30$) after 24 months ($P<0.05$) respectively. HbA1c was $6.3 \pm 1.3\%$ at baseline ($n=111$), $6.0 \pm 1.1\%$ at 6 months ($n=94$, $P<0.01$), $6.1 \pm 1.0\%$ at 12 months ($n=74$, $P<0.05$), and $5.7 \pm 0.6\%$ at 24 months ($n=29$, $P=\text{ns}$). Details about the course of glucose and HbA1c levels as well as changes in antidiabetic medication in the 56 patients of the ITT population with diabetes mellitus at baseline are given in Table 2.

Patients-assessed acromegaly symptom questionnaire (PASQ)

The PASQ was completed in 62 patients at baseline and in 56 of these patients also after 6 months. Significant improvements (t -test, exploratory) after 6 months were found for soft tissue swelling (2.9 ± 2.4 vs 2.1 ± 2.2 , $P<0.01$), general physical condition (4.6 ± 2.4 vs 3.7 ± 2.1 , $P<0.001$), headache (2.8 ± 2.5 vs 1.8 ± 2.1 , $P<0.01$), joint pain (3.5 ± 2.7 vs 2.9 ± 2.3 , $P<0.05$), and the total score (18.1 ± 9.9 vs 14.5 ± 9.0 , $P<0.01$).

No significant differences were found after 6 months for excessive sweating (3.0 ± 2.4 vs 2.6 ± 2.1), fatigue (3.7 ± 2.4 vs 3.2 ± 2.4), and numbness or tingling of limbs (2.3 ± 2.3 vs 1.3 ± 1.8). At 12 and 24 months, PASQ data were available from only 29 and 14 patients respectively.

Safety analysis

Safety analysis was performed in all 229 patients with median treatment duration of 51.9 weeks (mean $\pm$ s.d. = 51.8 ± 35.8 weeks). In total, non-serious adverse events (AEs) or serious adverse events (SAEs) regardless of a suspected causal relationship to pegvisomant were reported in 112 patients (48.9%). In 62 patients (27.1%), AEs ($n=50$) or SAEs ($n=27$) with a potential causal relationship with pegvisomant treatment were reported. Table 3 shows the AEs and the SAEs that occurred in $>1\%$ of patients, and were considered potentially treatment related by the respective treating physician. AEs without a potential causal relationship and an incidence $>1\%$ included gastrointestinal events, gallstone disease, musculoskeletal disorders, nervous system disorders, and infections. SAEs, which were not considered treatment-related, included death due to cardiac disease ($n=3$, 2 with preexisting cardiomyopathy and heart failure, 1 with myocardial infarction) and other cardiac events (myocardial infarction, tachyarrhythmia, angina ($n=4$), cholecystectomy ($n=7$), death due to a newly diagnosed glioblastoma ($n=1$), newly diagnosed colon cancer ($n=1$), squamous cell carcinoma of the lung ($n=1$), and renal cell carcinoma ($n=1$)). There was one pregnancy reported during pegvisomant treatment. Treatment was stopped immediately. The pregnancy has been terminated for other reasons in the 12th week of gestation. In 18

Figure 2 Pegvisomant doses in the group of patients with normal insulin-like growth factor-I (IGF-I) at the 12-month visit ($n=89$, left panel) and in the group with non-normalized IGF-I levels ($n=35$, right panel).

patients (7.9%), treatment with pegvisomant was discontinued due to AEs or SAEs, in five patients (2.2%), the dose was reduced or the treatment was temporarily discontinued. Injection site reactions ($n=17$, Table 3) include eight events of erythema and swelling at the injection side which occurred between 14 and 44 days after the start of pegvisomant treatment. Treatment was discontinued in one patient and interrupted for 6 days in another patient.

In the other patients, the reaction was reversible either spontaneously, after changing the injection site or local antiallergic treatment. In nine patients, the injection site reactions were increased in local fat tissue which occurred slowly. The drug was withdrawn in one of these cases. No follow-up data are available until now on whether the reactions disappeared. Headaches were reported in four cases (1.7%). In three of these patients, somatostatin analogs have been discontinued 1, 5, and 6 months earlier. An increase of tumor volume as the cause of headache was excluded by pituitary imaging in all cases. Transaminases above the upper limit of normal were reported in 21 patients and more than three times the normal range in 12 of these patients (5.2%). Details of 6 out of these 12 patients have recently been reported elsewhere (11). Transaminase

elevations occurred between 7.1 and 93.9 weeks after the start of pegvisomant, all had been pretreated with somatostatin analogs, five had gallstone disease at the time of onset of AE, and in all but two cases, ALT was the enzyme most elevated (peak ALT-elevation, 3.0–19.5 times the upper limit of normal). In two patients, γ -GT was the enzyme most elevated with peak elevations of 6.7 and 15.6 times the upper limit of normal. During follow-up, transaminases returned to normal in all but one patient after 4–32 weeks. In 7 out of 12 cases, the elevations were transient with normalization during continued pegvisomant treatment; in 4 out of 12 cases, transaminases normalized after treatment discontinuation; and in 1 out of 12 cases, γ -GT levels decreased, but remained elevated during continued drug treatment. This patient had increased γ -GT levels already before the start of treatment with pegvisomant. Follow-up MRI examinations were done at the responsible physicians' discretion. At the 12-month visit, the results of at least one MRI scan after the start of pegvisomant were available in 102 out of 128 (79.7%) patients. Overall, an increase in pituitary tumor size was reported by the treating physician in 12 cases between 7.6 and 67.4 weeks (median=48.3 weeks) after the start of pegvisomant

Table 2 Course of 56 patients with diabetes mellitus at baseline.

	Baseline ($n=56$)	6 Months ($n=56$)	12 Months ($n=40$)	24 Months ($n=18$)
IGF-I (x-fold ULN)	1.93 ± 1.17	$1.21 \pm 0.74^{\S}$	$1.07 \pm 0.87^{\S}$	$0.97 \pm 0.56^{\dagger}$
Fasting plasma glucose (mg/dl)	150 ± 68	133 ± 68	$119 \pm 46^{*}$	$104 \pm 21^{*}$
HbA1c (%)	7.2 ± 1.5	$6.6 \pm 1.4^{*}$	$6.5 \pm 1.1^{\dagger}$	6.0 ± 0.9
Treatment of diabetes mellitus (%)	76.8	71.4	67.5	50.0
(diet/oral antidiabetic drugs/insulin)				
• Oral antidiabetic drugs (%)	21.4	21.4	17.5	5.6
• Insulin (%)	26.8	23.2	22.5	22.2
• Insulin + oral antidiabetic drugs (%)	5.4	5.4	5.0	5.6

IGF-I, insulin-like growth factor-I; ULN, upper limit of normal. $^{*}P<0.05$, $^{\dagger}P<0.01$, $^{\S}P<0.0001$ (paired t -test for change to baseline). IGF-I was expressed as x-fold the upper limit of normal.

Table 3 Adverse events (AEs) and serious adverse events (SAEs) with an incidence >1% and a suspected causal relationship with pegvisomant according to the treating physician (safety, *n*=229).

	AE, <i>n</i> (%)	SAE, <i>n</i> (%)
Injection site reactions (erythema, swelling, lipohypertrophy)	17 (7.4)	–
Elevated liver enzymes	9 (3.9)	12 (5.2) ^a
Increase of pituitary tumor volume	–	12 (5.2) ^b
Headache	4 (1.7)	–

^aSeven of these patients had spontaneous normalization of transaminase elevation during continued pegvisomant treatment.

^bIncludes two cases, where no potential causal relationship was reported by the treating physician.

treatment. MRI scans of these patients were reevaluated by an independent neurosurgeon by serial analysis of all available scans during long-term follow-up of each individual patient. The neurosurgeon was blinded for the previous interpretations of the MRI scans and for intervention data (i.e. previous treatments, start of pegvisomant therapy). In 5 out of 12 cases, significant increases in tumor volume could not be verified at reevaluation. In 3 out of 12 patients, a slow and steady increase in tumor volume was observed and verified during long-term follow-up. In all of these three patients, tumor growth was already present before the start of pegvisomant treatment and did not change rate of progression thereafter. In four cases, an increase in tumor volume after the start of pegvisomant was verified. Two of them were not clinically relevant and two were most obvious, the result of a rebound from somatostatin-induced shrinkage, since it reexpanded to the size before the start of somatostatin analogs and showed no further growth thereafter. Details of all 12 cases are given in Table 4.

Discussion

The GH receptor antagonist pegvisomant is an important new drug added to our armamentarium for acromegaly treatment. Its high efficacy shown in clinical studies is

particularly important for patients with persisting disease activity, despite the use of all other non-medical and medical treatment options (2, 6–8). Since long-term experience with pegvisomant is limited, this study adds important information on safety and efficacy of pegvisomant in the field conditions of clinical practice. In this non-interventional, observational study, indication for pegvisomant treatment, treatment dosage, and follow-up were at the discretion of the treating physicians alone. Therefore, the data reflect clinical practice rather than a controlled clinical study. In addition, with more than half of the patients treated in small non-university centers and with more than 85% of all German patients treated with pegvisomant documented in the study, the data also reflect the current patient care in Germany. A possible drawback of this non-interventional study design is that all follow-up procedures were at the discretion of the responsible physicians' decision. In consequence, some parameters like PASQ scores, glucose levels, and even IGF-I values are not available in all patients and a bias in the reported treatment effects cannot be excluded. However, since underreporting can be expected primarily in patients with less severe disease, a major impact on study results seems to be unlikely. The patients included in GPOS were patients with long-standing disease, who in the majority had several previous treatments for acromegaly, including surgery, radiation therapy, as well as drug therapy with dopamine agonists and somatostatin analogs. In most patients, the indication for starting pegvisomant treatment was either a persistently elevated IGF-I level during treatment with somatostatin analogs or side effects of somatostatin analog treatment. According to the results from clinical studies (6–8), in most patients, pegvisomant treatment resulted in a significant decrease of IGF-I levels and, in parallel, the improvement of clinical signs and symptoms of acromegaly. However, IGF-I normalization rates in the GPOS were lower than those reported in previous clinical studies (7, 8). This may be explained in two ways. The first is that almost all patients included in a closely monitored and queried clinical trial have a better compliance in contrast to those in a surveillance study

Table 4 Reports of tumor volume increase in 229 patients included in German Pegvisomant Observational Study.

	Non-medical pretreatment	Medical pretreatment	MRI revaluation	Action taken with pegvisomant
1	Surgery and radiation	SSA, DA	Documented tumor growth before the start of pegvisomant	Withdrawn
2	Surgery (3×) and radiation	SSA, DA	Documented tumor growth before start of pegvisomant	Continued
3	Surgery (2×) and radiation	SSA, DA	Tumor growth could not be verified at reevaluation	Continued
4	Surgery	SSA, DA	Documented tumor growth before start of pegvisomant	Continued
5	–	SSA, DA	Tumor growth could not be verified at reevaluation	Continued
6	Surgery	SSA	Slight tumor growth during pegvisomant without clinical relevance	Continued
7	–	SSA	Rebound from somatostatin-induced shrinkage	Withdrawn
8	–	SSA, DA	Tumor growth could not be verified at reevaluation	Continued
9	Surgery	SSA	Slight tumor growth during pegvisomant without clinical relevance	Continued
10	Surgery (2×)	SSA, DA	Tumor growth could not be verified at reevaluation	Continued
11	Surgery and radiation	SSA	Tumor growth could not be verified at reevaluation	Continued
12	Surgery	SSA	Rebound from somatostatin-induced shrinkage	Withdrawn

MRI, magnetic resonance imaging; SSA, somatostatin analog; DA, dopamine agonist.

using the field conditions of clinical practice. The other possible reason is that, in contrast to controlled clinical trials, here dose titration of pegvisomant treatment did not follow a preassigned dosing algorithm and was not finalized in a significant number of patients. After 12 months of treatment, 42.8% of the patients with elevated IGF-I levels still had daily pegvisomant doses of 10 or 15 mg, i.e. had not yet reached the maximum dose. Since it is well known from pharmacodynamic data (6) that the onset of action of pegvisomant is rapid and 75% or more of the maximal reduction in serum IGF-I concentrations occurs within 2 weeks after the initiation of therapy, these data strongly support the assumption of a dose titration, that is inadequate to normalize IGF-I. However, even if an effective pegvisomant dose has been reached and the IGF-I levels were within the normal range, pegvisomant doses were increased during follow-up in approximately 50% of patients. This may be at least in part explained by the well-known fact, that after discontinuation of somatostatin analogs and after reaching an effective pegvisomant dose, a reincrease of IGF-I levels may occur due to the progressive clearance of somatostatin analogs (8). The clinical implication of this observation is that IGF-I must be regularly followed during pegvisomant treatment even after normal levels have been reached. The slight but significant decrease of mean fasting plasma glucose levels in the overall cohort supports recent data of improved glycemic control in patients after conversion from somatostatin analog to pegvisomant treatment (8, 12, 13). This is even more evident in patients with diabetes mellitus at baseline. In this subgroup, a significant improvement of plasma glucose and HbA1c levels were seen, accompanied by a reduction in antidiabetic medication. The safety profile of pegvisomant as documented in this database is similar to that shown in clinical studies. Elevation of transaminases to more than thrice the upper limit of normal was an occasional side effect of pegvisomant treatment and was seen in the present series in 12 patients (5.2%). All these patients were previously treated with somatostatin analogs. Therefore, the elevations of transaminases might either be the result of biliary sludge or be the concrement formation, which after resumption of normal gall bladder contractility following discontinuation of long-acting somatostatin analog treatment, may be propelled into the bile duct, or the result of a direct pegvisomant-induced effect (11). Interestingly, in some patients, transaminases normalized spontaneously during continued pegvisomant treatment. The clinical implications of these observations are, that liver function tests have to be regularly followed on pegvisomant treatment and, if transaminase elevations occur, biliary complications, which may arise from restitution of normal gall bladder motility after cessation of somatostatin analog treatment, need to be differentiated from pegvisomant-induced abnormalities. Increases in tumor volume have been reported in 12 patients (5.2%), but could be confirmed after thorough reevaluation in only

seven cases (3.1%). For three of them (1.3%), reevaluation with interpretation of all available scans during long-term follow-up by a blinded investigator revealed that these tumors were already steadily growing before the start of pegvisomant treatment and during somatostatin analog treatment. One of these patients was not pretreated with radiation therapy possibly influencing the risk of long-term tumor progression (7, 14). Two patients showed most obviously a rebound after somatostatin induced tumor shrinkage – one of these patients was not pretreated with surgery or radiotherapy. Two had a slight increase in tumor size without clinical relevance that might also be explained by tumor reexpansion after somatostatin analog treatment was stopped. Since, according to the literature, <1% of patients have failure to control tumor growth by radiotherapy and another 2.2% of patients are reported to show continuous growth during somatostatin analog treatment (14), the data do not provide evidence for an increased rate of tumor growth with pegvisomant treatment. In conclusion, the data from this observational study, which at present represents globally the largest database of patients on pegvisomant treatment, add important information to our knowledge about pegvisomant treatment in clinical practice. Pegvisomant is generally well tolerated with a safety profile similar to that reported in clinical trials and can effectively reduce IGF-I levels in patients with acromegaly refractory to conventional therapy.

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