Pituitary tumor size in acromegaly during pegvisomant treatment: experience from MR re-evaluations of the German Pegvisomant Observational Study

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Abstract

In treatment-resistant patients with acromegaly, pharmacotherapy with pegvisomant (Somavert) is a highly effective option. However, safety concerns have been raised related to a potential increase in tumor size during long-term pegvisomant treatment. Therefore, neuroradiological monitoring of tumor extension and volume was performed in the German Pegvisomant Observational Study, which covers 87% of patients treated with pegvisomant in Germany. As of 15 July 2007, a total of 307 patients (156 males and 151 females) had been included in the study and were on pegvisomant therapy for an average of 86.7 weeks. Median and mean doses of pegvisomant were 15 and 16.6 mg/day respectively. Out of these 307 patients, 18 were reported to have tumor-size increases as adverse events. From these 18 patients, all available serial magnetic resonance images were collected. Identical or similar sequences were chosen and the region of interest was magnified and compared across time after the best possible fit had been achieved by size and gray-scale correction. All available images were carefully re-evaluated according to this method. In 10 out of the 18 patients, there was no evidence of tumor-size increase, when the pre-treatment scans were compared with the most recent follow-up investigations. In two out of the remaining eight patients, there was a rebound effect observed after withdrawal of somatostatin analog treatment, but no further progression. In another three out of the eight patients, tumor-size increase had already been documented before pegvisomant treatment was commenced, during preceding somatostatin analog treatment and continued therapy. In the last three patients, tumor progression after the start of pegvisomant treatment was confirmed. All three patients had undergone pituitary surgery as primary treatment, but had not been pre-treated with radiotherapy. In all three cases, the tumor increase was not considered clinically significant and the investigators decided to continue pegvisomant treatment. In conclusion, in this large group of pegvisomant-treated patients, tumor progression was rare. It was reported in between 2 and 3% of patients treated, and did not exceed the expected rate in patients with acromegaly not treated with pegvisomant. In over one-half of patients, reports of tumor increase could not be confirmed by re-evaluation. This was mostly due to non-identical gantry projections. Misjudgements mainly occurred when only images from two individual investigations, rather than the entire series of scans, were compared. Thus, we recommend a careful serial evaluation of all available images to avoid misinterpretations and erroneous alerts. As from this presently largest database of acromegalic patients treated with pegvisomant, tumor-growth rate appears not to be different from patients on other treatment modalities. Although these data are reassuring with regard to the concern of somatotroph adenoma growth under peripheral GH receptor blockade, further study is required.

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Introduction

Acromegaly is a chronic endocrine disease characterized by excessive GH secretion and consequently elevated insulin-like growth factor-1 (IGF1) plasma levels, occurring in more than 98% 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 primary treatment of choice. Medical therapy with dopamine agonists or somatostatin analogs is an adjunctive treatment option in case of inadequate...
disease control (1, 2). For the past few years, pegvisomant (Somavert), a pegylated recombinant analog of human GH which acts functionally as a GH receptor antagonist, has now been available as an additional and highly efficient treatment option in patients with resistance to or intolerance of somatostatin analogs (3, 4).

Since pegvisomant acts on peripheral tissue and does not affect the pituitary tumor itself, an increased rate of tumor growth is considered a potential risk of long-term pegvisomant treatment. We have recently reported on safety and efficacy data from the German Pegvisomant Observational Study (GPOS), a non-interventional, surveillance study of patients treated with pegvisomant (5, 6). In this paper, we report a detailed analysis of those patients in whom an increase in tumor volume was reported as an adverse event and discuss the implication of these data on medical treatment of acromegaly.

Materials and methods

German Pegvisomant Observational Study

GPOS is an observational, multi-center, surveillance study to monitor safety and efficacy of pegvisomant, which comprises non-interventional data collection in accordance with the standard management of patients with acromegaly in everyday practice and in the respective sites. It was started in January 2004 and uses a protocol that is similar to the protocol of ACROSTUDY, the Pfizer Inc. (New York, USA) international database on pegvisomant treatment in acromegaly. Details of the study and results of previous interim analyses (data close December 20th 2005 and August 1st 2006 respectively) have been reported recently (5, 6). The study has been approved by the Independent Ethics Committee of the Charité Universitätsmedizin, Berlin, Germany, and all patients gave their written informed consent.

Subjects

Until July 15th 2007, 307 patients with acromegaly (156 men, 151 women, age 50.3 ± 13.9 years, mean ± S.D.) were enrolled in the study, comprising 87% of all pegvisomant prescriptions in Germany and thus being a highly representative sample. Age at diagnosis of acromegaly was 41.5 ± 13.0 years, indicating an average 8.8 years history of disease at time of inclusion in the study. All 307 patients have received at least one dose of pegvisomant and were all included in the safety analysis. Mean treatment duration was 86.7 ± 56.5 weeks.

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 female, 15 and 60 years old at baseline, macroadenomas) and one patient had McCune–Albright Syndrome (male, 15 years old at baseline). In addition, there was one patient suffering from familial acromegaly (male, 33 years). Two hundred and sixty-nine patients (87.6%) had previous pituitary surgery, 124 had previous radiation therapy (40.4%), and 287 patients (93.5%) had previous medical therapy for acromegaly with either dopamine agonists (n = 157) octreotide (n = 269), lanreotide (n = 32), and/or pegvisomant (n = 29, within clinical trials) before inclusion into the GPOS.

Two hundred and seventy-six patients passed a 6-month visit, 232 a 12-month visit, 153 a 24-month visit, 81 a 36-month visit, and 19 a 48-month visit.

Treatment with pegvisomant

The mean dose of pegvisomant at the time of the sixth interim analysis (data close 15 July 2007) was 16.6 ± 7.4 mg/day (median 15.0 mg/day). Thirty patients received a dose above 30 mg/day. At time of the sixth interim analysis, 26 patients were treated with pegvisomant (mean dose ± S.D.: 13.9 ± 8.5 mg/day) in combination with long-acting somatostatin analogs. Out of these patients, 18 received octreotide LAR (15 with 30 mg/month, 1 with 20 mg/month, and 1 with 10 mg/month; mean dose 27.2 ± 6.7 mg/month). 2 patients lanreotide autogel, 120 mg/month, and 6 patients received s.c. octreotide in doses between 50 µg and 500 µg/day (mean 308 ± 215 µg/day). The mean duration of somatostatin analog treatment was 15.9 ± 12.1 months.

MRI evaluations

Documented visits in the observational study are at baseline, 6 and 12 months after the start of pegvisomant, and yearly thereafter. Baseline and follow-up MRI examinations were done at the responsible physicians’ discretion. All MRI evaluations reported have been performed and interpreted by local neuroradiologists without using a standardized protocol.

An MRI examination was documented in GPOS at baseline in 244 patients (79.5%) and during follow-up in 230 patients (74.9%). If an increase in tumor volume was reported as an adverse event during the course of the study, all available MRI scans of this individual patient – regardless of whether there was a baseline or follow-up MRI documented in the database – including those scans before pegvisomant treatment were re-evaluated by an independent neurosurgeon, who was blinded for the previous interpretations of the MRI scans and for intervention data (i.e., previous treatments, the start of pegvisomant treatment). Identical or similar sequences were chosen, gray scales were corrected, and
the region of interest was magnified and compared across time after the best possible fit had been achieved by size and gray-scale correction. All available images were carefully re-evaluated according to this method.

**Laboratory analyses**

Serum IGF1 levels were measured in the local laboratories and were interpreted according to the local, age-dependent reference ranges, as previously described (5). Endogenous GH concentrations in the presence of pegvisomant were analyzed by a specific assay free of interference by the drug as described previously (7, 8). Serum concentrations of pegvisomant were determined by an immunofluorometric sandwich-type assay involving two monoclonal antibodies named 10A7 and 6F1, raised against hGH and retaining high cross-reactivity with pegvisomant (9).

**Results**

**Baseline characteristics and MRI evaluations during pegvisomant treatment**

The size of the pituitary tumor or residual adenoma at baseline before pegvisomant treatment was classified to be larger than 10 mm in diameter in 203 out of the 307 patients (66.1%) and smaller than 10 mm in diameter in 29 patients (9.4%). Fifteen patients (4.9%) had no visible tumor, six patients (2.0%) had a visible tumor without data on tumor size, and in 54 patients (17.6%) no data about baseline pituitary imaging were available.

**Patients with suspected increase in tumor volume**

An increase in pituitary tumor volume was reported by the responsible investigator as an adverse event in 18 out of 307 patients (5.9%; nine males and nine females, age 51.0 ± 15.8 years (mean ± S.D.) between 7.6 and 67.4 weeks (mean 41.1 ± 18.6 weeks) after the start of pegvisomant treatment. In ten of these cases (55.6%), increases in tumor volume could not be verified at re-evaluation. Figure 1 shows an example. As a consequence of the alert raised by the local neuroradiologist, in three patients treatment with pegvisomant was discontinued. In one patient, therapy was re-instituted after re-evaluation of the images. In eight patients (44.4%), an increase in tumor volume was confirmed at re-evaluation (four males and four females, age 43.5 ± 16.6 years (mean ± S.D.); Table 1). None of these patients were on combination treatment with somatostatin analogs.

The long-term courses of tumor volume in these eight patients can be classified as follows:

- Steady increase in tumor volume during long-term follow up: in three (two males and one female, age 27, 47, and 31 years: 35.1 ± 10.8 years (mean ± S.D.)) out of these eight patients, a slow and steady increase in tumor volume was observed and verified during long-term follow-up, irrespective of the treatment applied. Figure 2 shows an example. All these patients had undergone surgery and two had also received radiation therapy (LINAC, multiple fractions). Before the start of pegvisomant treatment, all of these three patients had received somatostatin analogs (duration of treatment 120.9 ± 73.5 weeks (mean ± S.D)). At the time when the tumor volume increase was reported as an adverse event, these patients were under pegvisomant for a mean duration of 11.5 ± 4.9 months (mean ± S.D.) with a final dose at onset AE of 18.3 ± 2.9 mg/day (mean ± S.D.). IGF1 levels were normalized in one case, and still elevated in two cases. Treating physicians decided to withdraw pegvisomant treatment in one case and continued treatment in the other two cases.
• Re-expansion of tumor volume without further growth thereafter: in two out of the eight patients (one male and one female, age 50 and 72 years), an increase in tumor size was noted 6 and 7 months after the start of pegvisomant respectively, which was most obvious the result of a rebound from somatostatin-induced shrinkage. One patient was primarily treated with octreotide, since she refused surgery and was, because of the invasive nature of her tumor, considered a candidate unlikely to achieve control of disease by transsphenoidal operation (Fig. 3). The other patient had undergone a transsphenoidal operation, but some intrasellar tumor and an asymmetrical suprasellar component persisted. Both cases had shown a tumor size reduction during pre-treatment by somatostatin analogs and, after switching treatment to pegvisomant, the tumor re-expanded to the size before the start of somatostatin analogs and showed no further growth thereafter. The last injection of a long-acting somatostatin analog was applied 8 and 7 months before the tumor size increase was reported. The latest pegvisomant doses in these two cases were 10 and 15 mg/day respectively. IGF1 levels were normalized in both. Tumor volume change was minor in both cases. However, in one case, pegvisomant treatment was discontinued and in the other case pegvisomant treatment was re-instituted after re-evaluation of the images.

• Tumor growth after the start of treatment with pegvisomant: in three cases (one male and two females, age 30, 30, and 60 years), a clinically not relevant tumor growth occurred 14.2 ± 1.5 months after initiation of pegvisomant treatment (Fig. 4). Pegvisomant doses in these patients were 23.3 ± 11.5 mg/day (mean ± S.D.). IGF1 levels were normalized in one case and elevated in two cases. Two patients were pre-treated by transsphenoidal surgery, one by transcranial surgery, but none of them had previous radiotherapy. Tumor–volume changes were minor. Growth was directed into the tumor cavities created by previous surgeries and thus was considered not clinically relevant. Consequently, pegvisomant treatment was continued in all three cases.

Analysis of potential risk factors associated with pituitary tumor growth

To analyse whether risk factors exist which are associated with tumor growth in the patient population investigated, several clinical and biochemical parameters were compared between the six patients with either steady increase in tumor volume during long-term follow-up or documented tumor growth after the start of pegvisomant treatment and the 222 patients who had a MRI examination during follow-up but no
documented increase in tumor volume. Patients with re-expansion of the tumor after somatostatin analog withdrawal (n=2) were not included in this analysis. The results are shown in Table 2.

Course of endogeneous GH levels

The course of endogeneous GH levels could be evaluated in seven out of eight patients with confirmed increase in tumor size (two with steady increase in tumor volume during long-term follow-up, two with tumor re-expansion, and three with tumor growth after the start of pegvisomant treatment) and in 280 out of 307 patients without a reported tumor-size increase. In one subject with slight tumor growth after the start of pegvisomant treatment, endogenous GH level was relatively low (12.6 ng/ml), but also pegvisomant concentration was low (6900 ng/ml), suggesting inadequate compliance. In the other six subjects, pegvisomant concentrations reached levels above 20 000 ng/ml (25 067 ± 1967 ng/ml, range 22 300–27 350 ng/ml). Corresponding endogenous GH concentrations in these six subjects with tumor size increase were 79.7 ± 24.3 ng/ml (range 60.4–127.0 ng/ml). In the group of all other patients with no reported increase in tumor size, but with similar pegvisomant serum concentrations (n=44, pegvisomant concentrations 20 000–30 000 ng/ml), mean endogenous GH concentrations were significantly lower (32.7 ± 26.8 ng/ml (range 2.9–159.5 ng/ml), P=0.0005). All six patients with an increase in tumor size, but only six out of 44 (13.6%) patients without tumor size increase had endogeneous GH levels during pegvisomant treatment above 60 ng/ml. Since baseline GH values before the start of pegvisomant treatment were available only in a very limited...
number of subjects, the changes in GH values as related to tumor growth could only be assessed in a minority of the entire cohort. In patients with no reported increase in tumor size ($n \geq 18$), endogenous GH levels increased approximately three times after initiation of pegvisomant treatment (median 327%, range 88–4457%). In patients with tumor size increase ($n = 3$), endogenous GH reached levels more than 10 times higher than at baseline (median 1258%, range 868–2437%).

**Discussion**

The GH receptor antagonist pegvisomant is an important and highly efficient drug added a few years ago to medical treatment options for acromegaly. Soon it was noted that the drug could normalize IGF1 levels in almost all patients treated, if only the dose was adequately adapted. 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 (3, 4). However, since pegvisomant does not act at the pituitary level and thus is not tumoricidal, it was feared that along with lowering of IGF1 levels, progression of the GH-secreting adenoma could occur. Similarities with feedback pituitary tumors that progress rapidly and aggressively if the primary therapy is directed against the peripheral glands were anticipated, in analogy with thyroid-stimulating hormone-secreting adenomas (10) and Nelson’s syndrome (11). A progression of two tumors documented in an initial study assessing long-term effects of pegvisomant administration (4) alerted physicians. Other reports of tumor-size increase followed (9, 12–15). Moreover, unusually high-proliferation markers reported in the histological workup of a GH-secreting tumor biopsy following pegvisomant treatment (16) seemed to justify this concern. Except for one patient, whose tumor progression occurred during combination therapy with pegvisomant and somatostatin analogs (15), all hitherto reported tumor-size increases were observed during monotherapy with pegvisomant (5, 9, 12–14).

### Table 2 Analysis of potential risk factors for tumor growth.

<table>
<thead>
<tr>
<th>Documented tumor growth ($n=6$)</th>
<th>No tumor growth reported/documentd ($n=222$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (males/females)</td>
<td>3/3</td>
<td>114/110</td>
</tr>
<tr>
<td>Age (years, at the start of pegvisomant)</td>
<td>37.6±13.2</td>
<td>50.9±13.2</td>
</tr>
<tr>
<td>History of pituitary surgery</td>
<td>6 (100%)</td>
<td>199 (88.9%)</td>
</tr>
<tr>
<td>History of radiotherapy</td>
<td>2 (33.3%)</td>
<td>94 (42.0%)</td>
</tr>
<tr>
<td>Pegvisomant dose (mg/day, last visit)</td>
<td>20.8±8.0</td>
<td>17.0±7.3</td>
</tr>
<tr>
<td>IGF1</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Baseline (µg/l)</td>
<td>633±194</td>
<td>500±259</td>
</tr>
<tr>
<td>(x-fold ULN)</td>
<td>2.1±0.8</td>
<td>1.9±1.0</td>
</tr>
<tr>
<td>Last visit (µg/l)</td>
<td>358±173</td>
<td>248±165</td>
</tr>
<tr>
<td>(x-fold ULN)</td>
<td>1.1±0.4</td>
<td>0.9±0.5</td>
</tr>
<tr>
<td>Endogeneous GH (ng/ml, last visit during pegvisomant)</td>
<td>79.7±24.3$^b$</td>
<td>32.7±26.8$^c$</td>
</tr>
</tbody>
</table>

$^a$Patients with either steady increase in tumor volume during long-term follow-up or documented tumor growth after the start of pegvisomant. Patients with re-expansion of the tumor after somatostatin analog withdrawal ($n=2$) were not included in this analysis.

$^b$Results from six patients, where data were available and where serum pegvisomant concentrations were 20 000–30 000 µg/l.

$^c$Results from 44 patients, where data were available and where serum pegvisomant concentrations were 20 000–30 000 µg/l.
The present study summarizes the experience in the largest cohort of patients to date observed during pegvisomant therapy. In this study, only in a small minority of patients, tumor progressions were described.

Increases in tumor volume were suspected in 18 patients (5.2%) and reported to health authorities as adverse events, but could be confirmed after careful re-evaluation in only eight cases (3.1%). For three of them (1.3%), re-evaluation with interpretation of all available scans during long-term follow-up by a blinded investigator revealed that these tumors were already steadily growing before pegvisomant treatment was commenced, and in one of these an increase in tumor volume was documented during somatostatin analog treatment. One of these patients was not pre-treated with radiation therapy possibly influencing the risk of long-term tumor progression (14, 17, 18). Two patients showed most obviously a rebound after somatostatin-induced tumor shrinkage – one of these patients was not pre-treated with surgery or radiotherapy. Since somatostatin analogs affect some degree of tumor size reduction in many patients (19–21) and discontinuation of the drugs has been shown to be associated with tumor size re-increase, the minor volume increase that was observed in these two patients cannot be attributed to pegvisomant, but rather to the discontinuation of somatostatin analogs. Three other patients had a slight increase in tumor size without clinical relevance. In all three of these, treatment was continued. Just like in the volumetric MR analysis reported by Jimenez et al. (14), there were a few patients whose tumor had already grown before exposure to pegvisomant and continued to grow during pegvisomant and after discontinuation of the GH antagonist. In these, there was no evidence that the continuing volume increase in the tumor could be attributed to pegvisomant.

Notably, in six out of the seven patients where data were available, endogenous GH concentrations during pegvisomant treatment were significantly higher than in patients without evidence for tumor growth. Since no baseline levels of endogenous GH were available, this may either be due to already higher baseline GH before the start of pegvisomant treatment or a more pronounced increase in endogenous GH during treatment. Despite the inter-individual variability of endogenous GH levels during pegvisomant treatment, the current data indicate that monitoring endogenous GH concentrations may be a clinically useful parameter during treatment with pegvisomant – provided a specific GH assay with no interference from pegvisomant is available (7, 8). Moreover, changes in GH levels and tumor volume would certainly be more interesting than basal values. In most patients unfortunately, no baseline serum was available for determination of endogenous GH. Thus, no statistically reliable correlation could be established. In the few patients assessed, we found higher levels of endogenous GH than in patients with similar pegvisomant concentrations, but stable tumors. The small number of observations for the change of endogenous GH levels in relation with adenoma expansion obviously limits this to a pilot observation, which merits further investigation in a higher number of cases. More data are necessary to finally assess the clinical significance of these findings.

Since according to the literature, <1% of patients have failure to control tumor growth following radiotherapy and another 2.2% of patients are reported to show continuous growth during somatostatin analog treatment (17), the data derived from this study do not provide evidence for an increased rate of tumor growth with pegvisomant treatment.

It might seem surprising that in only a minority of patients in whom tumor progression was suspected from comparing MR films during treatment, a volume increase was confirmed upon careful re-evaluation. Earlier investigators have described the problems and pitfalls of interpretation of post-operative MR images (22–26). Non-identical sequences and sections, varying magnifications, contrast or gray scales, and post-operative artefacts impede the comparison of residual tumor size and volume. Reconstruction of the sellar floor by various implants and mucosa regenerates and pneumatization deficits within the sphenoid sinus represent a specific problem following transsphenoidal surgery. Only a serial analysis of all available pre- and post-operative images with best possible fit regions of interest of all available investigations provides the most representative impression on whether surgery was radical or not and of the real consequent tumor-size development. Blinding of the investigator to therapies, as performed in this serial analysis of scans, is a most necessary pre-requisite for such determinations. With these techniques applied, the initial alert could be corrected in 10 out of 18 cases with suspicion of tumor growth. The progression rates determined in this study were much lower than the progression of non-secreting pituitary tumors observed in another study with a similar MR analysis protocol, but a most unfavourable bias in patient selection (27). A limitation of our study is the fact that we had only an opportunity to reveal falsely positive but not falsely negative reported imaging studies. We did not re-evaluate MR images from all patients of the entire study, and thus there is no certainty that each and every tumor progression was correctly recognized. The concern remains that the standards of radiology, which have falsely suspected tumor expansion, could, for the same reasons, have failed to detect tumor enlargement in other patients. We could, however, verify that all patients were monitored by repeat MRI and computed tomography (CT) studies respectively, and thus estimate that the error in this respect, if at all, is minor.

In conclusion, the data from this observational study, which at present globally represent 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 IGF1 levels in patients with acromegaly refractory to conventional therapy. Our data suggest that the risk of pegvisomant-induced tumor size progression is low. However, further prospective evaluation of this issue should continue with a standardized MR protocol in large databases of patients treated with GH receptor antagonists.

Declaration of interest

Daniel Weigel and Martin Bidlingmaier declare no potential conflicting interests. Michael Buchfelder, Michael Droste, Klaus Mann, Günter-Karl Stall and Christian J Strasburger are members of the International German Acrostoody Board. Christian J Strasburger is also a member of the National Acrostoudy Board. Katja Brübach and Bernard Saller are currently employed by Pfizer.

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