

# Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist

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## Summary

**Background** Pegvisomant is a new growth hormone receptor antagonist that improves symptoms and normalises insulin-like growth factor-1 (IGF-1) in a high proportion of patients with acromegaly treated for up to 12 weeks. We assessed the effects of pegvisomant in 160 patients with acromegaly treated for an average of 425 days.

**Methods** Treatment efficacy was assessed by measuring changes in tumour volume by magnetic resonance imaging, and serum growth hormone and IGF-1 concentrations in 152 patients who received pegvisomant by daily subcutaneous injection for up to 18 months. The safety analysis included 160 patients some of whom received weekly injections and are excluded from the efficacy analysis.

**Findings** Mean serum IGF-1 concentrations fell by at least 50%: 467 µg/L (SE 24), 526 µg/L (29), and 523 µg/L (40) in patients treated for 6, 12 and 18 months, respectively ( $p < 0.001$ ), whereas growth hormone increased by 12.5 µg/L (2.1), 12.5 µg/L (3.0), and 14.2 µg/L (5.7) ( $p < 0.001$ ). Of the patients treated for 12 months or more, 87 of 90 (97%) achieved a normal serum IGF-1 concentration. In patients withdrawn from pegvisomant ( $n = 45$ ), serum growth hormone concentrations were 8.0 µg/L (2.5) at baseline, rose to 15.2 µg/L (2.4) on drug, and fell back within 30 days of withdrawal to 8.3 µg/L (2.7). Antibodies to growth hormone were detected in 27 (16.9%) of patients, but no tachyphylaxis was seen. Serum insulin and glucose concentrations were

significantly decreased ( $p < 0.05$ ). Two patients experienced progressive growth of their pituitary tumours, and two other patients had increased alanine and aspartate aminotransferase concentrations requiring withdrawal from treatment. Mean pituitary tumour volume in 131 patients followed for a mean of 11.46 months (0.70) decreased by 0.033 cm<sup>3</sup> (0.057;  $p = 0.353$ ).

**Interpretation** Pegvisomant is an effective medical treatment for acromegaly.

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See Commentary 1743

## Introduction

Current treatments for acromegaly, which is usually caused by an adenoma of the pituitary, attempt to control the disease by reducing growth hormone secretion from the tumour either by surgery, radiotherapy, or medication. Unfortunately, when strict biochemical criteria are applied, surgery cures only 60% of patients overall, and less than half of patients with macroadenomas, which represent most cases seen.<sup>1,2</sup> The role of radiotherapy remains limited owing to slow onset of effect, ineffectiveness in normalising IGF-1 concentrations, and a high occurrence of panhypopituitarism.<sup>3–5</sup> Current medical therapy is also less effective than desired. Dopamine agonists rarely normalise growth hormone and IGF-1, and have side-effects that limit long-term tolerability and compliance.<sup>6,7</sup> Somatostatin analogues, such as octreotide or lanreotide, bind to somatostatin receptors present on the tumour, and inhibit growth hormone secretion. However, IGF-1 is normalised in only about 65% of patients.<sup>8–11</sup>

Pegvisomant (B2036-PEG; Sensus Drug Development Corporation, Austin, TX, USA) is a new, genetically-engineered analogue of human growth hormone which functions as a highly selective growth hormone receptor antagonist.<sup>12,13</sup> In a 12 week, placebo-controlled study,<sup>14</sup> clinical symptoms were significantly improved and serum IGF-1 concentrations normalised in 89% of acromegalic patients treated with pegvisomant. However, serum growth hormone concentrations also increased substantially in compensation, raising the questions of whether additional increases in serum growth hormone concentrations might occur if treatment was prolonged, whether a sustained increase in serum growth hormone might overcome the receptor-blocking action of the drug (ie, induce tachyphylaxis), or whether the increase in growth hormone might be accompanied by growth of the pituitary tumour.<sup>15</sup> The long-term efficacy of pegvisomant is also thought to be compromised by the development of antibodies to growth hormone or to pegvisomant. We report here the results of an analysis of the long-term safety and efficacy of pegvisomant in 160 patients with acromegaly treated for up to 18 months.

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## Patients and methods

### Patients

We screened patients with acromegaly, aged 18 years or older, at the participating clinics. At the first screening visit treatment with somatostatin analogues and dopamine agonists was discontinued in the patients receiving these drugs. A second screening visit took place a minimum of 2 weeks after discontinuation of somatostatin analogues and 5 weeks after discontinuation of dopamine agonists. Patients were eligible for enrolment if their serum IGF-1 concentration at that visit was at least 1.3 times the upper limit of the age-adjusted normal range, according to local laboratory values. The study protocols were approved by the human research committee at each site, and all patients gave written informed consent before confirmation of eligibility.

### Methods

Patients received pegvisomant as a once daily subcutaneous injection according to one of two clinical protocols (SEN-3613A and SEN-3614/15). 38 patients initially received weekly dosing (protocol SEN-3611/13) before being switched to daily dosing (protocol SEN-3613A). Only their daily dosing data are included in the efficacy analysis. Patients participating in protocol SEN-3614/15 received only daily dosing.

Daily dosing in both protocols began at 10 mg per day and was titrated up or down as necessary in 5 mg per day increments until the patient's serum IGF-1 concentration was normal or a maximum dose of 40 mg per day was reached. In SEN-3613A, the minimum dose titration interval was 2 weeks after the last dosing change. In SEN-3614/15, the dose adjustment was permitted no sooner than 8 weeks after the last dosing change. The 12 week, placebo-controlled data for patients who initially received pegvisomant in protocol SEN-3614/15 have been previously reported.<sup>14</sup>

All data from patients with acromegaly exposed to pegvisomant in the clinical development programme were included in the safety analysis. Safety assessments included: serum concentrations of alkaline phosphatase, alanine aminotransferase, aspartate transaminase, lactate dehydrogenase, total bilirubin, blood urea nitrogen, creatinine, cholesterol, triglycerides, and haemoglobin; white blood cell count; and platelet count; electrocardiograms; chest radiographs; and vital signs. If a patient had a gap in pegvisomant administration of more than 1 month, each dosing period was treated separately for the purposes of evaluating clinical laboratory results; this situation occurred in 26 patients. Adverse events were recorded at each visit. Pituitary tumour volumes were assessed<sup>16</sup> by a single neuroradiologist (RKH) who was unaware of treatment assignment and dose of pegvisomant, using magnetic resonance imaging obtained at the baseline visit before pegvisomant treatment, and from the most recently obtained image at the cut-off date for the analysis.

To assess the effect of pegvisomant on serum concentrations of IGF-1 and growth hormone, patients from the two daily dosing protocols were placed in cohorts on the basis of whether they had completed at least 6, 12, or 18 months of continuous daily pegvisomant treatment at the time of data cut-off. The cohorts were constructed in a cumulative fashion, such that all the patients in the 18 month treatment cohort were also included in the 6 and 12 month cohorts, and the patients in the 12 month cohort were also included in the 6 month cohort. For all cohorts, the baseline visit was regarded as the visit that occurred immediately before starting pegvisomant therapy

in the initial study protocol. Age-adjusted normal limits for IGF-1 were used. Antibodies to growth hormone were measured at about monthly intervals throughout treatment in all patients. Because pegvisomant interfered with the assay, the measurement of pegvisomant antibodies was made in samples obtained after pegvisomant treatment had been discontinued for a month.

Serum IGF-1 was measured by a competitive binding radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Serum growth hormone was measured using antiserum saturated with B2036 (the protein component of pegvisomant) to eliminate cross-reactions with pegvisomant. The sensitivity of the assay was 0.5 µg/L, with an inter-assay coefficient of variation of 16% (Endocrine Sciences, Calabasas Hills, California, USA). Antibodies to growth hormone were measured by radioimmunoassay (Endocrine Sciences). Antibodies to pegvisomant were assessed in a semi-quantitative screening assay by use of radiolabelled pegvisomant and a polyethylene glycol precipitation system. The assays for serum IGF-1, growth hormone and antibodies to growth hormone and and pegvisomant were done by a single laboratory (Endocrine Sciences). Serum pegvisomant concentrations were measured by a specific radioimmunoassay (Phoenix International Life Sciences, Saint-Laurent, Quebec, Canada). All other clinical laboratory samples were analysed with standard commercial assays.

### Statistical analysis

The assumption of the normality of the IGF-1, growth hormone, insulin, glucose and glycated haemoglobin data was investigated by use of a Shapiro-Wilks test, in which the null hypothesis that the data represented a random sample from the normal distribution was rejected. Therefore, the Wilcoxon's signed rank test, which is a non-parametric analogue to the paired-difference *t* test, was used for assessing the statistical significance of the changes from baseline for these measures.

### Role of the funding source

The study was financed and designed by Sensus Drug Development Corporation, Austin, Texas, USA.

## Results

167 patients with acromegaly participated in the pegvisomant clinical development programme. Seven of these patients received only placebo and are not otherwise reported here. Three of the remaining 160 patients received only a single dose of the drug, and five received only weekly doses (range 30–80 mg per week) during the course of early phase II studies. Although included in safety analysis, these patients' efficacy data have been excluded from this report. Table 1 shows the patients' demographic characteristics and acromegaly treatment before enrolment in the initial pegvisomant study. Of the 160 patients exposed to pegvisomant, 30 withdrew prematurely (two for protocol violations, nine for adverse events, five for lack of efficacy, two lost to follow up, and 12 as voluntary withdrawals). There were no clinically significant differences in demographics or prior treatment histories for the cohorts. However, the mean serum IGF-1 and growth hormone concentrations at baseline were substantially higher for the cohort of patients treated for more than 18 months than for the group as a whole (160), reflecting the more severe nature of the disease in the patients entered in the earliest phase of clinical development. The group as a whole accumulated 186

Characteristics	All patients (n=160)	Daily dosing			
		All (n=152)	6 month cohort (n=131)	12 month cohort (n=90)	18 month cohort (n=39)
Age, years†	46±14	46±14	46±14	44±13	42±13
Men	94 (59%)	87 (57%)	75 (57%)	47 (52%)	18 (46%)
Women	66 (41%)	65 (43%)	56 (43%)	43 (48%)	21 (54%)
Duration of disease, years†	8 (8)	8 (8)	8 (8)	8 (7)	8 (8)
Previous therapy					
Surgery	134 (84%)	130 (86%)	111 (85%)	82 (91%)	35 (90%)
Radiation	94 (59%)	89 (56%)	78 (60%)	57 (63%)	26 (67%)
Somatostatin analogue	117 (73%)	112 (74%)	97 (74%)	74 (82%)	33 (85%)
Dopamine agonist	76 (48%)	73 (48%)	67 (51%)	48 (53%)	19 (48%)
Bodyweight, kg†	94 (21)	94 (21)	94 (21)	93 (20)	92 (19)
Growth hormone, µg/L†	10·2 (16·0)	10·4 (16·3)	10·9 (17·0)	13·2 (19·7)	19·2 (27·0)
IGF-1 µg/L†	762 (330)	755 (327)	760 (306)	806 (297)	847 (321)
Pituitary tumour volume, cm³†	2·39 (3·45)	2·36 (3·48)	2·14 (2·47)	2·44 (2·70)	2·49 (2·58)

†Values are means (SD).

Table 1: **Baseline clinical and biochemical characteristics**

patient-years of exposure to pegvisomant, with a mean treatment duration of 425 days.

The dose-titrated decreases in serum IGF-1 concentrations required by the protocols was achieved in the three cohorts (figure 1). The mean serum pegvisomant trough concentrations were 12·25 mg/L (SE 0·73) in patients treated for 6 months, 17·57 mg/L (1·28) in those treated for 12 months, and 19·06 mg/L (2·82) in those treated for 18 months. The mean doses were 14·7 mg per day (0·4), 18·0 mg per day (0·7), and 19·6 mg per day (1·4), respectively. Normal serum IGF-1 concentration was achieved in 87 of 90 (97%) of patients treated for 12 months or more. Figure 2 shows the lowest value of serum IGF-1 concentration achieved during pegvisomant treatment for this cohort. To assess durability of the pegvisomant response (presence or absence of tachyphylaxis), an analysis of the 38 patients treated daily with pegvisomant for an average of 83 weeks showed that the serum IGF-1 concentrations were within normal limits in 572 of the 624 post-baseline visits (91·7%). Mean serum growth hormone concentrations at baseline were 10·9 µg/L (SE 1·5), 13·2 µg/L (2·1), and 19·2 µg/L (4·3) in the 6, 12, and 18 month cohorts. On average, these increased by 12·5 µg/L (2·1), 12·5 µg/L (3·1), and 14·2 µg/L (5·7) to 23·1 µg/L (3·1), 25·6 µg/L (4·3), and 33·8 µg/L (8·6), respectively ( $p<0·05$  for within-cohort, baseline *vs* final comparisons), with the time course of the increases mirroring the falls in serum IGF-1 concentrations (figure 1). In a subgroup of patients who were withdrawn from pegvisomant and not placed on alternative medical therapy for at least one month ( $n=45$ ), the mean serum growth hormone concentration was

8·0 µg/L (2·5) at baseline, rose to 15·2 µg/L (2·4) at the last visit before withdrawal, and fell back within 30 days of withdrawal to 8·3 µg/L (2·7) ( $p=0·6739$  compared with baseline).

27 patients (16·9%) had one or more samples test positive for antibodies to pegvisomant. 11 of these 27 patients had only single increases in titres ranging from 1:4 to 1:16. Three patients who had sustained low titres of antibodies to growth hormone normalised their serum IGF-1 concentration within 2 months of beginning treatment; their IGF-1 concentrations remained normal despite persistent, low antibody titres. In the remaining 13 patients, antibodies to growth hormone appeared sporadically during the course of therapy. In 39 patients, samples were taken about 1–2 months after stopping pegvisomant treatment (as confirmed by serum pegvisomant assay) and were analysed for pegvisomant antibodies. Samples from ten patients tested positive in titres ranging from 1:8 to 1:256. In all of these patients, antibodies to growth hormone were also present, either during or after treatment. Nine of these patients normalised their IGF-1 and none showed evidence of tachyphylaxis.

Fasting serum insulin concentrations fell from 23·0 mU/L (SE 4·1) to 15·8 mU/L (3·6) in the 6 month cohort ( $p=0·0717$ ), from 23·0 mU/L (4·1) to 12·4 mU/L (2·5) in the 12 month cohort ( $p=0·0075$ ), and 23·3 mU/L (6·3) to 12·4 mU/L (2·2) in the 18 month cohort ( $p=0·0393$ ). Fasting serum glucose concentrations also decreased from 1053 mg/L (74) to 862 mg/L (19·8) in the 6 month group ( $p=0·0130$ ), from 1053 mg/L (74) to 906 mg/L (23) in the 12 month group ( $p=0·0531$ ), and 984 mg/L (34) to 904 mg/L (21) in the 18 month cohort ( $p=0·0125$ ). The glycated haemoglobin concentrations did not change significantly (from 5·7% [0·1], 5·7% [0·1], and 5·4% [0·1] to 5·7% [0·1], 5·8% [0·1], and 5·7% [0·1], respectively).

Adverse effects reported in more than 10% of the patients are displayed in table 2. Injection-site reactions were reported by 18 patients (11%) and were generally characterised as mild, erythematous, self-limited reactions that did not require treatment. The infections reported were generally non-serious, upper-respiratory-tract infections that rarely required treatment, with the exception of seven cases of pneumonia, a gluteal abscess, and a case of urosepsis. Two patients had increased concentrations of alanine aminotransferase, and aspartate transaminase of more than ten-fold above the upper limit of normal within 12 weeks of beginning pegvisomant therapy, and as a consequence were withdrawn. Both were symptom-free except for mild fatigue, and had

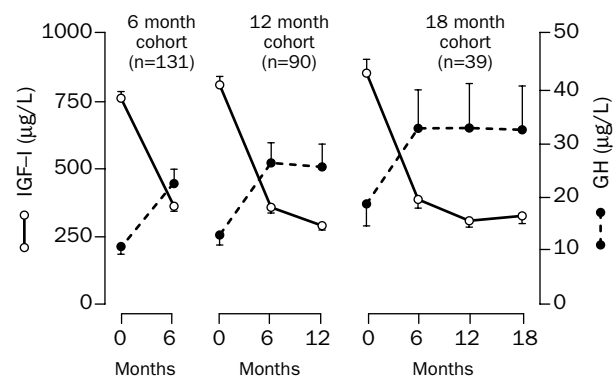


Figure 1: **Serum concentrations of insulin-like growth factor-1 and growth hormone**

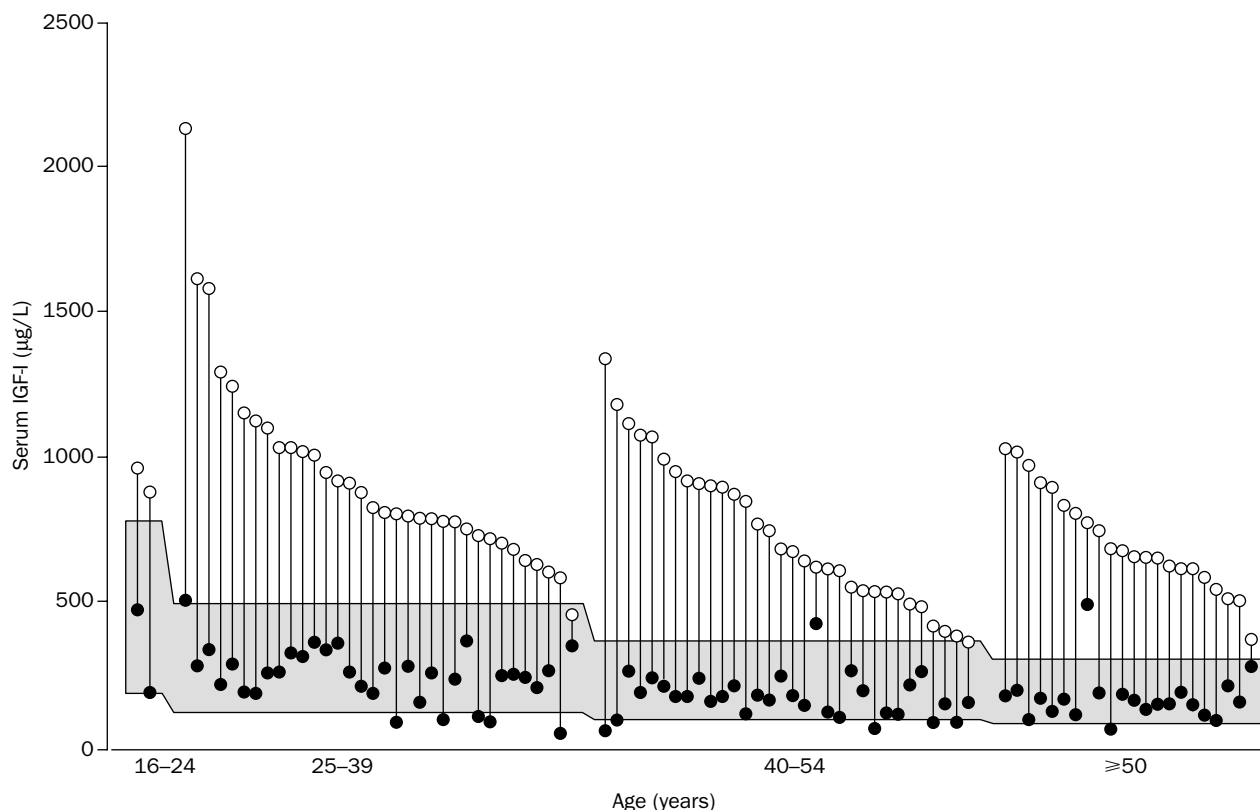


Figure 2: **Baseline and lowest values of individual serum insulin-like growth factor-1 concentrations achieved in 90 patients treated for 12 months or more with daily pegvisomant**

†p<0.05 vs baseline; ‡p<0.01 vs baseline. The shaded area represents the age-adjusted normal range for insulin-like growth factor-1.

normal bilirubin concentrations throughout. Liver enzyme concentrations returned to normal within several months after stopping the drug. As previously reported,<sup>14</sup> one of the two had a further rise in these enzyme concentrations on rechallenge with pegvisomant.

The mean serum concentrations of blood urea nitrogen, creatinine, bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, and triglyceride; haematocrit; white blood cell count; and platelet counts were within normal limits at baseline and did not change during treatment (data not shown). No clinically significant changes were noted in vital signs, electrocardiograms, or chest radiographs (data not shown). Mean total serum cholesterol concentrations at baseline (5.23 mmol/L [SE 0.08]) were above the recommended level for therapeutic intervention ( $\geq 5.14$  mmol/L), but did not change substantially during the course of pegvisomant treatment (5.18 mmol/L [0.11] in patients treated for >12 months). Hypercholesterolaemia was reported as an adverse event in 23 patients (table 2),

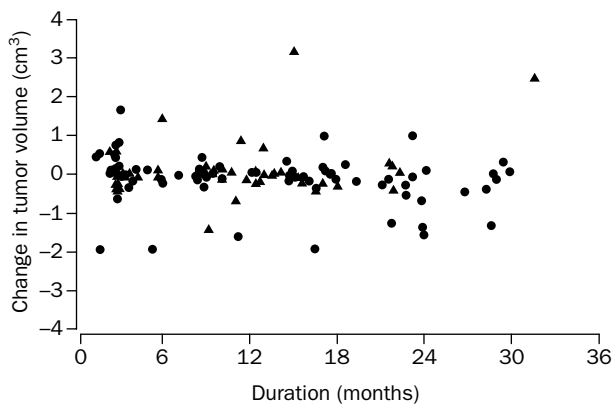
Description	n (%)
Headache	41 (26)
Infection	52 (33)
Accidental injury	28 (18)
Pain	36 (23)
Influenza-like syndrome	33 (21)
Injection site reaction	18 (11)
Back pain	21 (13)
Asthenia	21 (13)
Diarrhoea	23 (14)
Sinusitis	16 (10)
Hypercholesterolaemia	23 (14)
Arthralgia	19 (12)

Table 2: **Adverse effects occurring in at least 10% of patients treated with pegvisomant (n=160)**

although 18 of these patients had serum total cholesterol concentrations greater than 5.14 mmol/L at baseline.

Baseline magnetic resonance imaging (MRI) scans were available for 149 patients before treatment with pegvisomant: 59 (40%) had tumours smaller than 1 cm<sup>3</sup> at baseline. Paired sets of the baseline and the most recent scans were available for 131 patients. The mean tumour volume did not decrease significantly (2.41 cm<sup>3</sup> [SE 0.31] at baseline to 2.37 cm<sup>3</sup> [0.31], a mean change from baseline of -0.033 cm<sup>3</sup> [0.057]; p=0.353). The mean duration between baseline and final scan was 11.46 months (0.70). In 78 patients previously treated with radiation therapy the mean tumour volume decreased by -0.126 cm<sup>3</sup> (0.071) over 12.48 months (0.99; p=0.214). In 53 patients previously untreated with radiation therapy the mean tumour volume increased by 0.103 cm<sup>3</sup> (0.093) over 9.97 months (0.90; p=0.948). There was no association between the duration of pegvisomant treatment and change in tumour volume (figure 3). For all patients who had at least 12 months between their baseline and final scan, the results were similar with a mean change of -0.067 cm<sup>3</sup> (0.103; p=0.064).

Two patients required treatment owing to progression in tumour size, the cause of which was unclear. Both had large, globular tumours with impingement on the optic chiasm at baseline despite recent prior trans-sphenoidal surgery. The first patient had a baseline tumour volume of 5.53 cm<sup>3</sup> just before treatment. The tumour volume after 3 months of pegvisomant at 15 mg/day was 5.66 cm<sup>3</sup>. The patient was off pegvisomant for 6 months and then restarted, but unfortunately the MRI taken at the time of restart was found to have motion artefact, preventing an accurate calculation of tumour volume. At the next scheduled MRI examination 6 months later, the tumour



**Figure 3: Lack of association between duration of pegvisomant treatment and change in tumour volume on the most recent MRI scan obtained while on pegvisomant**

●=previous radiation therapy. ▲=no previous radiation therapy.

volume was 8.71 cm<sup>3</sup>, prompting treatment with radiotherapy. The second patient, who is the subject of a published case report,<sup>17</sup> had a baseline tumour volume of 2.93 cm<sup>3</sup> before treatment, and was treated with weekly doses of 80 mg pegvisomant for 3 months, during which time the tumour volume decreased to 2.75 cm<sup>3</sup>. The patient was then treated with octreotide for 5 months and subsequently switched back to pegvisomant. An MRI scan was not obtained until 2 months after the switch, at which time the tumour volume was calculated to be 4.28 cm<sup>3</sup>. A scan obtained 11 months after the restart of pegvisomant showed a tumour volume of 4.92 cm<sup>3</sup>. 16 months after the restart of pegvisomant, octreotide was added to the regimen because of the onset of visual symptoms and incomplete control of the patient's serum IGF-1 concentration. An MRI scan obtained at that time could not be used to calculate tumour volume. The next MRI scan, obtained 6 months after the start of combined pegvisomant and octreotide treatment, showed a tumour volume of 5.41 cm<sup>3</sup>. Pegvisomant was discontinued, resulting in a substantial rise in serum IGF-1 concentrations, accompanied by recurrence of headaches, fatigue, diaphoresis and other symptoms of active acromegaly, despite continued maximum doses of octreotide. The patient therefore underwent a second trans-sphenoidal procedure to debulk the tumour mass.

## Discussion

The size of the reduction in serum IGF-1 concentrations at 12 and 18 months was similar to that seen in patients treated with pegvisomant 20 mg/day in a prior, well controlled 12 week study.<sup>14</sup> The 97% response rate is high compared with the approximately 65% obtained with existing medical therapies such as dopamine agonists<sup>6,7</sup> and somatostatin analogues.<sup>8-11</sup> The greater size and predictability of the response is a result of pegvisomant's mechanism of action as a growth hormone receptor antagonist, in which the effect of excess growth hormone is blocked at a cellular level, thus reducing growth hormone action rather than relying on inhibition of growth hormone secretion from the tumour. The response to pegvisomant is therefore not dependent on tumour expression of fully functional somatostatin receptors,<sup>18</sup> nor is it affected by somatostatin receptor type-specificity.<sup>19</sup> A recent report has confirmed pegvisomant's effectiveness in patients with acromegaly resistant to dopamine agonists and somatostatin analogues.<sup>20</sup>

The rise in mean serum growth hormone concentrations temporally mirrored the fall in serum IGF-1 concentrations, and after the first observation made at 6 months, did not continue to increase (figure 1). This observation was similar to that made in the previous study,<sup>14</sup> in which the rise in growth hormone was seen at the first post-baseline visit, 2 weeks after initiation of pegvisomant therapy, with no significant subsequent rise. The mechanism responsible for the rise in growth hormone is unknown, although it might be related to the fall in serum IGF-1 concentrations since, in the subgroup of patients (n=45) who were withdrawn from pegvisomant and not placed on alternative medical therapy for 1 month, serum growth hormone concentrations fell back to baseline.

Mean pituitary tumour volumes did not change in patients followed up on average for 11.5 months, irrespective of the patients' previous history of radiation therapy. Although two patients required treatment due to progression in tumour size, there was no association between the duration of pegvisomant treatment and change in tumour volume. These observations form the basis for some optimism that patients treated with pegvisomant will not develop a Nelson's syndrome-like effect, in which interruption of growth hormone-mediated negative feedback on the tumour via blockade of the growth hormone receptor might result in later onset of tumour growth. However, because Nelson's syndrome can become apparent after many years, and because pituitary tumours in patients with acromegaly are usually slow-growing, long-term monitoring of tumour volumes using MRI scans is prudent in patients treated with pegvisomant, as would be the case with any patient with acromegaly treated medically.

Pegvisomant was generally well tolerated. The 30% rate of generally mild infections probably reflects the relatively long period of intense follow-up of these patients. However, since the data are uncontrolled, no firm conclusions can be drawn as to the potential for infection in patients treated with the drug. The observation that two patients had raised liver aminotransferases requiring discontinuation of the drug, suggests that caution is warranted and liver function should be monitored until a larger number of patients have been exposed to the drug. Since 11 of the 90 patients treated for more than 1 year had serum IGF-1 concentrations that fell below the lower limit of the age-adjusted normal range, with nine requiring a downward titration of their dose, IGF-1 should also be monitored frequently and the dose adjusted to keep the serum IGF-1 concentration within the normal range. In contrast, the serum growth hormone concentration is not a useful marker of disease activity status in pegvisomant-treated patients.

Other metabolic consequences of acromegaly could be improved by blocking the growth hormone receptor with pegvisomant. Excess growth hormone is associated with insulin resistance in animals, presumably as a result of interference with insulin signal transduction.<sup>21</sup> Patients with acromegaly are also insulin resistant,<sup>22</sup> and up to 30% of untreated patients with acromegaly have been reported to develop type 2 diabetes.<sup>23</sup> In the current analysis, fasting serum insulin and glucose concentrations fell significantly in patients treated with pegvisomant for up to 18 months, despite none of these patients being overtly diabetic at baseline. Pegvisomant has also been shown to influence the development of experimental diabetic nephropathy,<sup>24-27</sup> warranting further investigation of the drug's effects on insulin and carbohydrate metabolism in patients without acromegaly.

## Contributors

A van der Lely, M O Thorner, S Melmed, P J Trainer, A L Barkan, G M Besser, D R Clemmons and M L Vance formed the original investigator group. K A Zib, R J Davis, and J A Scarlett were responsible for the design, preparation and conduct of the study. S Hackett was responsible for the statistical design and analysis of the study. R K Hutson was responsible for the MRI analysis. J A Scarlett and A van der Lely prepared the original manuscript. All authors contributed to revision of the manuscript.

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