

## TREATMENT OF ACROMEGALY WITH THE GROWTH HORMONE-RECEPTOR ANTAGONIST PEGVISOMANT

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## ABSTRACT

**Background** Patients with acromegaly are treated with surgery, radiation therapy, and drugs to reduce hypersecretion of growth hormone, but the treatments may be ineffective and have adverse effects. Pegvisomant is a genetically engineered growth hormone-receptor antagonist that blocks the action of growth hormone.

**Methods** We conducted a 12-week, randomized, double-blind study of three different daily doses of pegvisomant (10 mg, 15 mg, and 20 mg) and placebo, given subcutaneously, in 112 patients with acromegaly.

**Results** The mean ( $\pm$ SD) serum concentration of insulin-like growth factor I (IGF-I) decreased from base line by  $4.0 \pm 16.8$  percent in the placebo group,  $26.7 \pm 27.9$  percent in the group that received 10 mg of pegvisomant per day,  $50.1 \pm 26.7$  percent in the group that received 15 mg of pegvisomant per day, and  $62.5 \pm 21.3$  percent in the group that received 20 mg of pegvisomant per day ( $P < 0.001$  for the comparison of each pegvisomant group with placebo), and the concentrations became normal in 10 percent, 54 percent, 81 percent, and 89 percent of patients, respectively ( $P < 0.001$  for each comparison with placebo). Among patients treated with 15 mg or 20 mg of pegvisomant per day, there were significant decreases in ring size, soft-tissue swelling, the degree of excessive perspiration, and fatigue. The score for total symptoms and signs of acromegaly decreased significantly in all groups receiving pegvisomant ( $P \leq 0.05$ ). The incidence of adverse effects was similar in all groups.

**Conclusions** On the basis of these preliminary results, treatment of patients who have acromegaly with a growth hormone-receptor antagonist results in a reduction in serum IGF-I concentrations and in clinical improvement. (N Engl J Med 2000;342:1171-7.)

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**A** CROMEGALY is a chronic debilitating disorder resulting from excessive secretion of growth hormone and a resulting increase in the production of insulin-like growth factor I (IGF-I). It is usually caused by somatotroph adenomas of the pituitary gland. The goal of treatment is to reverse the effects of the hypersecretion of growth hormone and normalize production of IGF-I. Effective treatment ameliorates the symptoms and signs of the disease and lowers the mortality rate.

The current treatments for acromegaly are surgical removal of the adenoma, radiation therapy, and drug

treatment. Among patients treated surgically, only 60 percent of patients overall and less than half of those with large tumors (the majority of patients) can be classified as cured according to strict biochemical criteria.<sup>1-4</sup> These low rates are presumably due to incomplete surgical resection. Radiation therapy is characterized by delayed effect, poor efficacy, and a high incidence of panhypopituitarism.<sup>5,6</sup> Dopamine-agonist drugs, such as bromocriptine and cabergoline, are effective in only a minority of patients, and their adverse effects limit tolerability and compliance.<sup>7-9</sup> Somatostatin agonists, such as octreotide, inhibit the secretion of growth hormone, but the secretion of growth hormone and the production of IGF-I are reduced to normal in only about 50 percent of patients.<sup>10-14</sup> These agonists also inhibit the secretion of insulin, glucagon, and several gastrointestinal hormones and can cause cholelithiasis.<sup>15</sup>

Pegvisomant is a genetically engineered analogue of human growth hormone that functions as a growth hormone-receptor antagonist.<sup>16,17</sup> We conducted a 12-week study of the efficacy and tolerability of pegvisomant in patients with acromegaly.

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## METHODS

### Patients

The diagnosis of acromegaly was established on the basis of symptoms and signs at presentation, evidence of a pituitary adenoma on computed tomography or magnetic resonance imaging of the pituitary fossa, and high serum concentrations of IGF-I. Of the 112 patients enrolled in the study, 93 had undergone pituitary surgery, of whom 57 had also been treated with conventional radiation therapy. Six patients had undergone irradiation without surgery, nine had received only drug therapy, and four had received no therapy. Patients who had received a long-acting somatostatin analogue within 12 weeks before enrollment were not eligible for the study.

### Protocol

The study protocol was approved by the human-research committee at each study site, and all patients gave written informed consent before eligibility was confirmed. At the first screening visit, therapy with somatostatin analogues and dopamine agonists was discontinued in the patients receiving such treatment. The second screening visit took place a minimum of two weeks after the discontinuation of somatostatin-analogue therapy and five weeks after the discontinuation of dopamine-agonist therapy. Patients were eligible for enrollment if their serum IGF-I concentration at the second screening visit was at least 1.3 times the upper limit of the age-adjusted normal range, according to local laboratory values.

Clinical and laboratory assessments were conducted at the two screening visits, at the base-line visit, and 2, 4, 8, and 12 weeks after the initiation of treatment. The assessments consisted of a history taking and physical examination; completion of a questionnaire designed to evaluate five symptoms and signs of acromegaly (soft-tissue swelling, arthralgia, headache, excessive perspiration, and fatigue), with scores ranging from 0 (no symptoms) to 8 (severe, incapacitating symptoms); measurement of serum growth hormone while the patient was fasting; measurement of serum IGF-I, free IGF-I, IGF-binding protein 3 (IGFBP-3), and the acid-labile subunit of IGFBP-3; and routine laboratory tests (measurement of hematologic values and serum chemistry values and urinalysis with microscopical evaluation). In addition, the ring size of the fourth digit of the right hand (or the fifth, if the fourth was too large) was measured with the use of 58 standardized European jeweler's rings (Jewel Toolcraft, Birmingham, United Kingdom), ranging in diameter from 12.5 mm to 25 mm. Magnetic resonance imaging of the pituitary and electrocardiography were performed and serum samples were obtained for assay for anti-growth hormone antibodies before the base-line visit and at the end of the study. Pituitary-tumor volumes were calculated from the magnetic resonance images<sup>18</sup> by a single evaluator who was unaware of the patients' treatment assignments. Adverse effects were recorded at each visit.

### Treatment

The patients were stratified according to the serum IGF-I concentration at the second screening visit (values 1.3 to 2.0 times the upper limit of the age-adjusted normal range vs. values >2.0 times the upper limit). The patients were then randomly assigned at the base-line visit to receive either pegvisomant (at a daily dose of 10 mg, 15 mg, or 20 mg) or a placebo. In order to decrease the amount of time needed to achieve steady-state serum pegvisomant concentrations, patients assigned to pegvisomant treatment received an 80-mg loading dose of the drug at the base-line visit, and the patients assigned to placebo received a loading dose of placebo.

Pegvisomant was prepared as a lyophilized powder containing 10 mg, 15 mg, or 20 mg of pegvisomant, 1.36 mg of glycine, 36 mg of mannitol, 1.04 mg of dibasic, anhydrous sodium phosphate, and 0.36 mg of monobasic sodium phosphate monohydrate. The placebo contained the same ingredients except for pegvisomant. Pegvisomant and placebo were reconstituted with 1 ml of water for injection and were self-administered as once-daily sub-

cutaneous injections for 12 weeks. The study was double-blinded, and only the statistician preparing the randomization schedule was aware of treatment assignments.

### Serum Assays

Serum IGF-I was measured by radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, Calif.), and serum free IGF-I by a two-site immunoradiometric assay (Diagnostic Systems Laboratory, Webster, Tex.). Serum IGFBP-3 was measured by radioimmunoassay (Endocrine Sciences, Calabasas Hills, Calif.) and the serum acid-labile subunit of IGFBP-3 by sandwich enzyme-linked immunosorbent assay (Diagnostic Systems Laboratory). Serum growth hormone was measured by radioimmunoassay (Endocrine Sciences), which was modified to avoid cross-reactivity with pegvisomant. Anti-growth hormone antibodies were measured by radioimmunoassay (Endocrine Sciences).

### Statistical Analysis

Continuous variables, including the primary efficacy end point (the percentage change in the serum IGF-I concentration from base line), other biochemical-efficacy variables (serum concentrations of free IGF-I, IGFBP-3, and the acid-labile subunit of IGFBP-3), and ring size were compared with the use of analysis of variance, with study sites pooled according to geographic area. An expanded statistical model incorporating a term for the interaction between treatment and center as well as covariates (e.g., base-line serum IGF-I and growth hormone concentrations, IGF-I values at study entry, sex, and base-line body weight) was used in the analysis of the primary efficacy variable.

We compared the frequency of normal serum IGF-I concentrations in the treatment groups at any time after base line and at 12 weeks, using a logistic-regression model with the independent variables of treatment, pooled study site, and base-line serum IGF-I concentration. At the other scheduled visits (at two, four, and eight weeks), we used a Cochran-Mantel-Haenszel test, with the data stratified according to pooled study site. Symptoms and signs were categorized as worse, unchanged, or improved, and the results in the treatment groups were compared with the use of the extended Cochran-Mantel-Haenszel test, with adjustment for pooled study site. All P values are two-sided.

## RESULTS

The base-line characteristics of the patients in the treatment groups were similar (Table 1). A total of 112 patients (63 men and 49 women) were enrolled and received study medication. The mean ( $\pm$ SD) age was  $48 \pm 14$  years, and the mean duration of acromegaly was  $8 \pm 8$  years.

Four patients withdrew from the study. One patient in the placebo group withdrew because of persistent headache (in this case, the outcome was classified as lack of efficacy). Another patient in the placebo group was withdrawn from the study after five days of treatment, after a review of his magnetic resonance image revealed a large pituitary adenoma displacing and compressing the optic chiasm. This patient had undergone no assessments of efficacy, and therefore his base-line data were not included in the efficacy analysis but were included in the safety analysis. A patient assigned to 15 mg of pegvisomant withdrew after one week of treatment because of persistent headaches (classified as lack of efficacy), and another patient in this group was withdrawn from the study at nine weeks because of high serum aminotransferase concentrations (described below).

TABLE 1. BASE-LINE CHARACTERISTICS OF PATIENTS WITH ACROMEGALY.\*

CHARACTERISTIC	PLACEBO	PEGVISOMANT		
		10 mg/DAY	15 mg/DAY	20 mg/DAY
No. of patients	32	26	26	28
Age — yr	50±15	47±12	46±15	48±13
Sex — M/F	19/13	15/11	14/12	15/13
Duration of disease — yr	8±8	8±7	8±7	8±7
Previous therapy — no. (%)				
Surgery	26 (81)	22 (85)	22 (85)	23 (82)
Conventional radiotherapy†	17 (53)	11 (42)	14 (54)	15 (54)
Gamma-knife radiotherapy	3 (9)	0	3 (12)	1 (4)
Somatostatin-analogue therapy	24 (75)	15 (58)	21 (81)	21 (75)
Dopamine-agonist therapy	17 (53)	15 (58)	9 (35)	14 (50)
Weight — kg	90.3±24.2	93.1±19.6	93.4±18.2	92.1±21.9
Body-mass index‡	30.6±4.6	31.2±6.2	31.9±5.7	30.2±5.8
Serum growth hormone — ng/ml	8.7±20.1	7.8±10.5	11.5±23.1	8.1±10.6
Serum IGF-I — ng/ml	670±288	627±251	649±293	732±205

\*Plus-minus values are means ±SD. IGF-I denotes insulin-like growth factor I. Most patients had received more than one type of previous therapy.

†This form of therapy included proton-beam irradiation.

‡The body-mass index is the weight in kilograms divided by the square of the height in meters.

TABLE 2. SELECTED MEASURES OF EFFICACY AND SAFETY IN THE PLACEBO AND PEGVISOMANT GROUPS.\*

VARIABLE	PLACEBO	PEGVISOMANT		
		10 mg/DAY	15 mg/DAY	20 mg/DAY
No. of patients	31†	26	26	28
Serum IGF-I				
Base line — ng/ml	670±288	627±251	649±293	732±205
12 wk — ng/ml	640±288	449±220	321±203	279±183
Percentage change from base line at 12 wk	-4.0±16.8	-26.7±27.9	-50.1±26.7	-62.5±21.3
P value for the comparison with placebo		<0.001	<0.001	<0.001
P value for the comparison with 10 mg of pegvisomant/day			0.005	<0.001
P value for the comparison with 15 mg of pegvisomant/day				0.02
Patients with normal serum IGF-I values at 12 wk — no. (%)	3 (10)	10 (38)	18 (75)‡	23 (82)
P value for the comparison with placebo		0.02	<0.001	<0.001
Patients with normal serum IGF-I values at any visit after base line — no. (%)	3 (10)	14 (54)	21 (81)	25 (89)
P value for the comparison with placebo		<0.001	<0.001	<0.001
Serum growth hormone				
Base line — ng/ml	8.7±20.1	7.8±10.5	11.5±23.1	8.1±10.6
12 wk — ng/ml	7.6±15.1	10.5±11.8	21.4±22.7	22.7±27.8
Change from base line at 12 wk — ng/ml§	-0.8±5.0	2.7±5.5	9.2±10.6	14.4±21.2
P value for the comparison with placebo		0.08	<0.001	<0.001
Tumor volume — ml				
Base line	1.9±1.8	2.4±2.6	3.3±6.1	2.1±1.9
12 wk	1.8±1.8	2.4±2.6	3.4±6.3	2.2±2.0
P value for the comparison with placebo		0.06	0.35	0.91

\*Plus-minus values are means ±SD. IGF-I denotes insulin-like growth factor I.

†Efficacy data are not included for one patient who withdrew from the study before the first evaluation after base line.

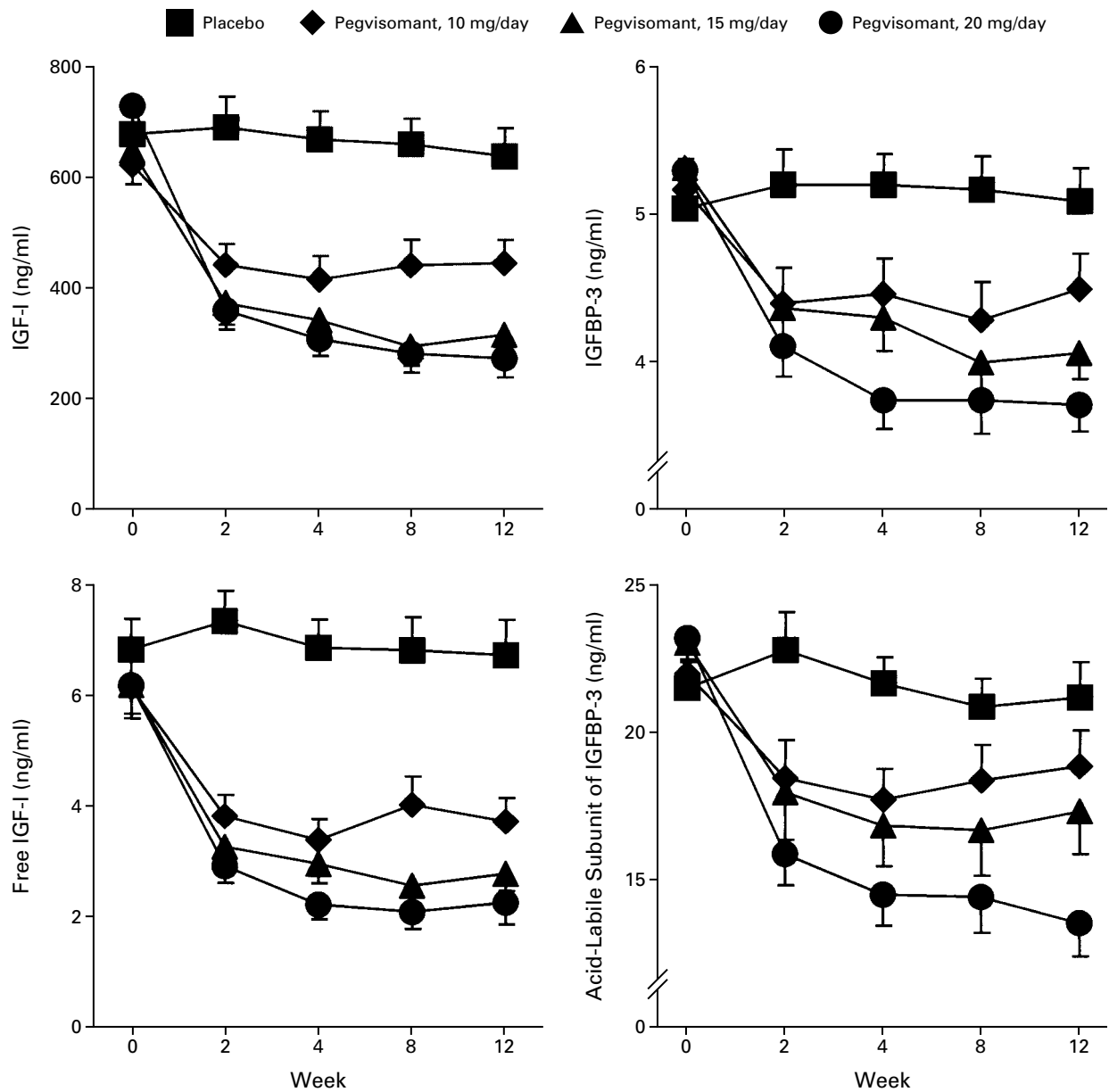
‡Two patients who withdrew from the study before week 12 were excluded from the analysis.

§Values are the means of individual changes.

**Efficacy**

Serum IGF-I concentrations decreased in all three pegvisomant groups, whereas the concentrations did not change appreciably in the placebo group (Table 2 and Fig. 1). No interactions of treatment with study site were detected. There was a dose-dependent increase in the frequency of normal serum IGF-I concentrations in the three pegvisomant groups (Table 2). Two of the three patients in the group receiving

20 mg of pegvisomant in whom the serum IGF-I concentration did not fall to normal had substantial decreases, from 1032 to 420 ng per milliliter in one patient (age-adjusted upper limit of normal, 360) and from 761 to 420 ng per milliliter in the other (age-adjusted upper limit of normal, 290). There were also dose-dependent reductions in serum concentrations of free IGF-I, IGFBP-3, and the acid-labile subunit of IGFBP-3 in the three pegvisomant groups (Fig. 1).



**Figure 1.** Serum Concentrations of Insulin-like Growth Factor I (IGF-I), Free IGF-I, IGF-Binding Protein 3 (IGFBP-3), and the Acid-Labile Subunit of IGFBP-3 in Patients with Acromegaly.

For all four measures, the values at all visits after base line (week 0) were significantly lower ( $P \leq 0.05$ ) in the three pegvisomant groups than in the placebo group. T bars indicate means  $\pm$  SE.

The mean scores for individual symptoms and signs and the mean total score increased slightly in the placebo group and decreased in all the pegvisomant groups (Table 3), with significant decreases in the scores for soft-tissue swelling, excessive perspiration, and fatigue and in the total score. The mean ring size at base line corresponded to a size "X" standard European jeweler's ring. The mean ( $\pm$ SD) ring size at 12 weeks had decreased by  $0.1\pm 2.3$  size in the placebo group, by  $0.8\pm 1.6$  size in the group receiving 10 mg of pegvisomant ( $P=0.16$  for the comparison with placebo), by  $1.9\pm 2.0$  sizes in the group receiving 15 mg ( $P=0.001$ ), and by  $2.5\pm 3.3$  sizes in the group receiving 20 mg ( $P<0.001$ ).

#### Serum Growth Hormone Concentrations, Anti-Growth Hormone Antibodies, and Tumor Volume

Serum growth hormone concentrations increased and then plateaued in the pegvisomant groups in a dose-dependent fashion that coincided with the magnitude and timing of the reduction in serum IGF-I concentrations (data not shown). The serum growth hormone concentrations at 12 weeks in the patients treated with 15 mg or 20 mg of pegvisomant per day were significantly higher than those of the patients in the placebo group (Table 2). Serum anti-growth hormone antibodies in titers ranging from 1:4 to 1:64 were detected in five patients treated with 10 mg of pegvisomant per day, one patient treated with 15 mg, and two patients treated with 20 mg. No patient had a significant change in tumor volume during the study, nor did the mean tumor volume change significantly more in any pegvisomant group than in the placebo group (Table 2).

#### Safety

Pegvisomant was well tolerated. The incidence of reported adverse effects was similar in all four study groups (Table 4). Injection-site reactions were reported by two patients receiving 10 mg of pegvisomant per day, one patient receiving 15 mg, and three patients receiving 20 mg and were characterized as mild, erythematous, self-limited reactions that did not require treatment. The only serious adverse effect was in a patient treated with 15 mg of pegvisomant who was withdrawn from the study because he had a serum alanine aminotransferase concentration of 904 U per liter (normal range, 0 to 47) and a serum aspartate aminotransferase concentration of 389 U per liter (normal range, 0 to 37) after eight weeks of treatment. The patient had mild fatigue, his serum bilirubin and alkaline phosphatase concentrations did not rise, viral serologic tests were negative, and ultrasonography of the liver was normal.

The abnormal serum enzyme values returned to normal within eight weeks after the discontinuation of the study drug but rose again after a four-week rechallenge with 10 mg of pegvisomant per day. This

**TABLE 3.** CHANGES IN SCORES FOR SYMPTOMS AND SIGNS OF ACROMEGALY.\*

VARIABLE	PLACEBO	PEGVISOMANT		
		10 mg/DAY	15 mg/DAY	20 mg/DAY
No. of patients	31†	26	25‡	28
Score for soft-tissue swelling				
Base line	2.1 $\pm$ 1.9	2.4 $\pm$ 2.4	2.7 $\pm$ 2.4	2.8 $\pm$ 2.3
Change at 12 wk	+0.3 $\pm$ 2.3	-0.7 $\pm$ 1.6	-1.2 $\pm$ 2.3	-1.3 $\pm$ 1.3
P value		0.12	0.05	<0.001
Score for arthralgia				
Base line	3.7 $\pm$ 2.0	3.0 $\pm$ 1.9	3.2 $\pm$ 2.5	2.8 $\pm$ 2.0
Change at 12 wk	+0.1 $\pm$ 1.8	-0.3 $\pm$ 1.8	-0.5 $\pm$ 2.5	-0.4 $\pm$ 2.1
P value		0.68	0.17	0.10
Score for headache				
Base line	2.1 $\pm$ 2.1	2.5 $\pm$ 2.2	3.0 $\pm$ 2.3	2.1 $\pm$ 1.9
Change at 12 wk	+0.1 $\pm$ 1.7	-0.4 $\pm$ 1.6	-0.3 $\pm$ 1.4	-0.3 $\pm$ 2.0
P value		0.58	0.62	0.24
Score for excessive perspiration				
Base line	3.1 $\pm$ 2.5	3.2 $\pm$ 2.2	3.8 $\pm$ 2.1	3.3 $\pm$ 1.9
Change at 12 wk	+0.1 $\pm$ 1.7	-0.6 $\pm$ 1.6	-1.1 $\pm$ 1.3	-1.7 $\pm$ 1.6
P value		0.21	0.003	<0.001
Score for fatigue				
Base line	3.2 $\pm$ 1.9	3.7 $\pm$ 1.9	4.3 $\pm$ 2.5	3.9 $\pm$ 2.0
Change at 12 wk	+0.7 $\pm$ 1.5	-0.5 $\pm$ 1.4	-1.3 $\pm$ 1.7	-1.0 $\pm$ 1.6
P value		0.03	<0.001	<0.001
Total score§				
Base line	14.2 $\pm$ 7.2	14.8 $\pm$ 8.2	17.0 $\pm$ 8.6	14.9 $\pm$ 6.7
Change at 12 wk	+1.3 $\pm$ 6.0	-2.5 $\pm$ 4.3	-4.4 $\pm$ 5.9	-4.7 $\pm$ 4.7
P value		0.02	0.004	<0.001

\*Plus-minus values are means  $\pm$ SD. Each of the symptoms and signs was rated on a scale of 0 (no symptoms) to 8 (severe, incapacitating symptoms). P values are for the comparison with the placebo group.

†Efficacy data were not included for one patient who withdrew from the study before the first evaluation after base line.

‡One patient did not speak English and therefore was not included in this analysis.

§The total score for symptoms and signs was based on a cumulative score of 0 to 40, equal to the sum of the five individual scores.

**TABLE 4.** ADVERSE EFFECTS THAT OCCURRED IN AT LEAST 10 PERCENT OF PATIENTS.\*

ADVERSE EFFECT	PLACEBO (N=32)	PEGVISOMANT		
		10 mg/ DAY (N=26)	15 mg/ DAY (N=26)	20 mg/ DAY (N=28)
		number of patients (percent)		
Upper respiratory tract infection	5 (16)	5 (19)	4 (15)	5 (18)
Headache	4 (12)	3 (12)	2 (8)	3 (11)
Injection-site reaction	0	2 (8)	1 (4)	3 (11)
Pain†	2 (6)	2 (8)	1 (4)	4 (14)
Diarrhea	1 (3)	1 (4)	0	4 (14)
Nausea	1 (3)	0	2 (8)	4 (14)
Flatulence	0	0	1 (4)	3 (11)

\*Some patients had more than one adverse effect.

†Pain included pain in the scalp, neck, shoulders, and arms and legs.

rechallenge was approved by the human-research committee, and the patient gave written informed consent. The values returned to normal once more after discontinuation of the drug. With the exception of the values for this patient, the mean serum alanine aminotransferase and aspartate aminotransferase concentrations did not increase significantly in any group during the study. No other patient had more than small, clinically unimportant changes in any laboratory test.

## DISCUSSION

The action of growth hormone is initiated by dimerization of the extracellular domain of the growth hormone receptor by a single growth hormone molecule.<sup>19</sup> Pegvisomant is an analogue of human growth hormone, with nine mutations that increase its affinity for one of the binding sites on the receptor and abolish binding to a second site, thereby preventing functionally correct dimerization of the receptor.<sup>17</sup> Because it is pegylated (polyethylene glycol polymers are covalently bound to the protein), it has a long biologic half-life, and the likelihood of antibody formation is low.<sup>20-23</sup> Pegvisomant is a highly selective ligand for the growth hormone receptor, and it does not cross-react with other receptors, including the prolactin receptor.<sup>24</sup> In contrast to the mechanism of action of dopamine-agonist drugs<sup>7-9</sup> and somatostatin analogues, agents that inhibit growth hormone secretion,<sup>10-13,25,26</sup> the efficacy of pegvisomant is independent of any characteristics of the somatotrophic tumor. Instead, pegvisomant blocks the ability of growth hormone to stimulate production of IGF-I, the main mediator of the somatotrophic actions of growth hormone.

In this 12-week, double-blind, placebo-controlled study, pegvisomant significantly ameliorated both the clinical and the biochemical manifestations of acromegaly. The onset of action of pegvisomant was rapid, with 75 percent or more of the maximal reduction in serum IGF-I concentrations occurring within 2 weeks after the initiation of therapy, and was sustained during the 12-week course of treatment. The contribution of the loading dose to this rapid onset of action is not known.

Pegvisomant was well tolerated; the incidence of adverse effects was similar in the placebo group and all three pegvisomant groups. Despite the possibility that pegvisomant treatment might lead to further increases in growth hormone secretion, and even to tumor growth, the increase in serum growth hormone concentrations was small, was not progressive, and was not associated with any evidence of tumor growth. Very low titers of anti-growth hormone antibodies were detected in the serum of only 8 of the 80 patients who were treated with pegvisomant. However, because of the relatively short duration of this study, as well as the occurrence of high serum aminotrans-

ferase concentrations in one patient, we suggest caution in the interpretation of the data on safety.

Longer treatment of more patients will be required before any conclusions can be drawn regarding the safety of the drug, including its effects on tumor size and hepatic function. However, given the efficacy and minimal adverse effects identified in this study, pegvisomant has the potential to become a useful medical treatment for acromegaly.

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