



Wassily Kandinsky (1866-1944). *Red Spot II*, 1921.

*Pegvisomant is a genetically engineered growth hormone-receptor antagonist that has shown promising results in normalizing serum insulin-like growth factor-I and controlling acromegaly with acceptable side effects.*

# Acromegaly: A New Therapy

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**Background:** *The treatment of acromegaly can be challenging. Despite a multimodality approach (surgery, radiation, dopamine agonists, somatostatin analogs), many patients do not achieve normalization of serum insulin-like growth factor I (IGF-I) concentrations.*

**Methods:** *The author discusses the characteristics and indications of pegvisomant therapy for patients with acromegaly and compares the use of this newly developed GH receptor antagonist with other pharmacological agents such as somatostatin and dopamine agonists.*

**Results:** *Therapy with pegvisomant allows serum IGF-I concentrations to be normalized in up to 97% of patients with acromegaly, including those who have failed other treatment modalities. With this agent, circulating GH levels increase as a result of the drop in IGF-I levels. The rise is rapid (within 2 weeks) and does not appear to be progressive over time.*

**Conclusions:** *Published studies have shown pegvisomant to have efficacy in the treatment of acromegaly. As it appears to be well tolerated and safe, this novel compound may be an important therapeutic option for patients with acromegaly. Additional study of this novel agent and its mode of action is warranted.*

## Introduction

Acromegaly is a relatively rare disease caused by the hypersecretion of growth hormone (GH). It almost always occurs as a result of a benign adenoma in the anterior portion of the pituitary gland. Patients with acromegaly have been reported to have an increased morbidity and mortality when compared with the general population.<sup>1-4</sup> The clinical manifestations of uncontrolled acromegaly include soft-tissue swelling, joint pain, nerve entrapment, glucose intolerance, hypertension, and cardiac disease.<sup>5-7</sup>

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Submitted February 25, 2002; accepted April 12, 2002.*

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*The drug used in the study is Sensus Drug Development Corp's  
Somavert brand of pegvisomant. Sensus was acquired by Phar-  
macia Corp in March 2001. Pharmacia has prepared regulatory  
filings for approval of Somavert in the United States and Europe.  
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The primary biochemical goal of acromegaly treatment is to restore the GH/IGF-I axis to normal. Because GH release is highly pulsatile, serum concentrations vary throughout the day. Thus, the use of random serum GH concentrations is not reliable to determine if acromegaly is present or adequately controlled. However, the GH-stimulated peptide insulin-like growth factor-I (IGF-I) is present in the serum in more steady concentrations. IGF-I represents an excellent integrative marker of total GH secretion and should therefore be used as the primary biomarker of acromegaly control. In adequately controlled patients, IGF-I levels should fall into the normal age- and gender-adjusted normal range.

## Treatment Options

The currently available treatment options for acromegaly are surgery, radiation therapy, medical therapy with dopamine agonists, or somatostatin analogs. Currently, the initial treatment for most patients is surgery via a transsphenoidal approach.<sup>8</sup> If patients have large tumors (>1 cm), the chance of a surgical cure is less than 50%.<sup>9</sup> Radiation therapy is sometimes used in those patients not cured by surgery. Radiation can be given either as a series of treatments over several weeks or as a single treatment (stereotactic radiosurgery). The major disadvantage of radiation therapy is the slow onset of action. It often takes many years to reach maximal levels of GH reduction. In fact, normalization of GH dynamics is achieved in only 25% to 50% of patients.<sup>1,10,11</sup> Side effects including panhypopituitarism and secondary tumors in the radiation field can also occur.<sup>12,13</sup>

Medical treatment for acromegaly includes dopamine agonists such as bromocriptine and cabergoline. In general, these agents are effective in less than 25% of patients with acromegaly.<sup>14,15</sup> More patients normalize IGF-I concentrations with somatostatin analogs than with dopamine agonists. Depending on the population selected, normalization rates range from 22% to 74%.<sup>16,17</sup> The mechanism of action of both the dopamine agonists and the somatostatin analogs is to bind to receptors on the GH-producing cells in the pituitary gland and decrease GH production. In the case of the dopamine agonists, the target is the D<sub>2</sub> receptor. In the case of the somatostatin analogs, the targets are two subtypes of the somatostatin receptor, sst2 and, to a lesser degree, sst5. It is thought that the dopamine agonists and somatostatin analogs are ineffective in many patients because not all tumors express fully functional sst2 and sst5 somatostatin receptors or D<sub>2</sub> dopamine receptors. Both the dopamine agonists and somatostatin receptors are not specific for recep-

tors expressed only in the pituitary gland. As a result, there are unintended effects on many tissues throughout the body. Common side effects of dopamine agonists are nausea and orthostatic hypotension. Common side effects of the somatostatin analogs include gastrointestinal disturbances such as abdominal pain, nausea, flatulence, and diarrhea.<sup>18</sup>

Despite the many modalities available to treat acromegaly, uncontrolled acromegaly occurs in a significant portion of patients, and thus new agents are needed to treat this disorder. The GH-receptor antagonists, a class of agents currently in late-stage clinical development, offer the potential to successfully treat a higher percentage of patients with acromegaly.

## Pegvisomant Therapy for Acromegaly

The prototype GH-receptor antagonist is a compound called pegvisomant. The structure of pegvisomant is similar to the native GH with the exception of 9 amino acid substitutions. These targeted substitutions permit the hormone to bind to the GH receptor without receptor activation. Thus, pegvisomant functions as a competitive antagonist, preventing normal endogenous GH from binding to its receptor. Pegvisomant has been demonstrated to have a dose-response profile as increasing amounts of drug occupy a greater percentage of possible binding sites. This allows for individualized patient doses based on serum IGF-I response and clinical symptoms.

Two published studies have examined the efficacy and safety of pegvisomant. A 12-week randomized, double-blind, placebo-controlled study found that pegvisomant therapy significantly decreased IGF-I concentrations and improved the signs and symptoms of acromegaly.<sup>19</sup> Treatment with 10-mg, 15-mg, and 20-mg pegvisomant resulted in normalized IGF-I concentrations in 54%, 81%, and 89% of patients, respectively. An

Characteristics of Pegvisomant

Class:	GH-receptor antagonist
Molecular Structure:	191 amino acids, addition of several polyethylene glycol moieties to increase half-life
Route of Administration:	Subcutaneous injection
Frequency:	Daily
Effective Dose:	5-40 mg/day
Efficacy:	Up to 97% IGF-I normalization <sup>20</sup>
Tumor Size:	Monitor as per routine
Safety Monitoring:	Periodic liver function tests

open-label extension study in which the pegvisomant was individually titrated demonstrated that longer ( $\geq 12$  months) treatment with pegvisomant resulted in normalized IGF-I concentrations in 97% of patients.<sup>20</sup>

In all clinical trials to date, pegvisomant has been well tolerated. There does not appear to be an increased risk of gastrointestinal disturbance, hyperglycemia, or arrhythmias that have been reported with the use of somatostatin analogs. Significant but reversible liver function abnormalities have been reported in a small number of patients ( $< 1\%$ ). Some of the principal characteristics of pegvisomant are summarized in the Table.

As a group, patients taking pegvisomant did not exhibit any evidence of tumor progression during the extended-treatment study.<sup>20</sup> Paired sets of baseline and posttreatment (mean 11.46 months) for 131 patients on pegvisomant therapy demonstrated no significant mean change in tumor volume over time ( $2.41 \text{ cm}^3 \pm .31$  at baseline vs  $2.37 \text{ cm}^3 \pm .31$  posttreatment). This was the case regardless of whether a patient received radiation therapy prior to the administration of pegvisomant. Within the 131 patient cohort, however, there were 2 tumors that demonstrated significant growth. As the natural history of some pituitary tumors is to grow aggressively, it is not unexpected that a small percentage would demonstrate an increase in size regardless of therapy. In a recent report, approximately 7% of tumors treated preoperatively with octreotide were found to progressively increase in size despite therapy.<sup>21</sup>

There is a rise in serum GH in acromegalic patients treated with pegvisomant. This appears to be related to the loss of negative IGF-1 inhibition on GH secretion rather than to any pathological process, including tumor growth. Accordingly, a similar phenomenon has been observed in normal individuals taking pegvisomant. The rise in serum GH levels is evident by 2 weeks of treatment. GH levels rapidly plateau, however, and remain stable, even after a prolonged treatment duration.<sup>20</sup> Again, as the rise in serum GH levels is not associated with growth of the pituitary tumor and the majority of GH-receptor sites are occupied by pegvisomant, the elevated circulating GH concentrations are not thought to be physiologically significant. Similar elevations in circulating ligand concentrations are observed when other antagonists are used (eg, estrogen levels increase with tamoxifen, testosterone levels increase with flutamide).

Currently, surgery is the initial therapy for acromegaly. The development of pegvisomant will not change this primary role for surgery. For patients not cured by surgery, however, the safety and efficacy pro-

file of pegvisomant indicates that it should be considered for use as first-line medical therapy. Additional clinical experience with the compound should provide the basis for refinement of therapeutic recommendations. For instance, there is currently no published experience regarding the use of this compound in a pediatric population or in women during pregnancy or the postpartum period. Also, the dose needs to be carefully monitored to keep IGF-I in the normal range to prevent GH deficiency condition caused by giving too much medication.

No other compounds intended for use in acromegaly are as far along in the drug development process as pegvisomant. Most of the potential therapies being examined are modifications of the currently available somatostatin analogs. The goal with these agents is to provide more potent activity at the somatostatin receptor subtypes that influence GH secretion. Thus, the use of these agents is dependent on the expression of the appropriate receptor by the tumor itself. Given the known tumor heterogeneity resulting in variability of somatostatin receptor expression and function, it is unlikely that this approach will result in agents that can match the efficacy levels seen with the GH-receptor antagonists.

## Conclusions

All of the currently available pharmacological agents, even those that act directly at the level of the tumor itself, do not generally result in destruction of the neoplastic tissue. The ideal agent would eradicate the tumor while sparing the surrounding normal tissue. To date, no such agents have been successfully developed. It is possible that future approaches, such as gene therapy, will deliver agents that are truly tumoricidal. Until these agents become available, compounds such as pegvisomant offer a significant therapeutic achievement: biochemical control of IGF-I in nearly all patients with acromegaly. This should allow the patients who do not respond to conventional therapy to avoid the chronic destructive complications of uncontrolled acromegaly.

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