

CLINICAL CASE SEMINAR

Control of Tumor Size and Disease Activity during Cotreatment with Octreotide and the Growth Hormone Receptor Antagonist Pegvisomant in an Acromegalic Patient

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ABSTRACT

We describe the case of an acromegalic subject, who was the first patient ever treated with the GH receptor antagonist pegvisomant. Furthermore, in this particular patient, progression in tumor size was encountered during treatment with pegvisomant. The patient de-

scribed did benefit from cotreatment with pegvisomant and octreotide, including decreased GH levels, normalization of serum insulin-like growth factor I concentrations, and improvement of visual field defects. (*J Clin Endocrinol Metab* 86: 478–481, 2001)

THIS 34-YR-OLD MALE patient was treated by transphenoidal selective adenectomy for a convex GH-producing pituitary macroadenoma in February 1997. He had, at that time, active acromegaly with fatigue, headaches, excessive perspiration, and joint pains. Before surgery, a single injection of 50 μ g octreotide sc decreased the serum GH concentration from 70 ng/mL to minimally 6 ng/mL after 6 h. Serum PRL was normal, whereas secondary hypothyroidism and hypogonadism were present. These were subsequently treated by replacement therapy. The neurosurgical procedure was unsuccessful because 6 months after operation the tumor still extended up to the optic chiasm, although without signs or symptoms of compression of the chiasm. Because of the extension close up to the optic chiasm, it was decided not to treat him with radiotherapy. Because of tumor size and persistent disease activity, he started treatment with octreotide in sc dosages up to 200 μ g three times daily (t.i.d.). This did not result in normalization of his serum total insulin-like growth factor I (IGF-I) concentrations (untreated IGF-I levels, \pm 230 nmol/L; age-adjusted upper normal level, <50 nmol/L; nadir in serum total IGF-I levels during treatment with octreotide 200 μ g sc t.i.d., 170 nmol/L). Therefore, it was concluded that this patient was only partially sensitive to octreotide.

In April 1997, he received for the first time pegvisomant,

as he participated as the first patient in a dose-finding study in our center. The pegvisomant dose administered was 0.3 mg/kg body weight (27.6 mg). A single sc administration of the GH receptor (GHR) antagonist resulted in a decline in the total serum IGF-I level on day 3 after the injection without reaching normal levels (from 233 nmol/L to 211 nmol/L).

In July 1997, he was enrolled in a Phase 2b study on the efficacy and safety of pegvisomant in the treatment of acromegaly. In this 6-week placebo-controlled study, he was randomized to receive 80 mg pegvisomant sc once weekly. A significant decrease in serum total IGF-I levels was observed (from 305 nmol/L to 190 nmol/L), although the result was still three times the upper age-adjusted normal level (<50 nmol/L).

Because temporarily no study drug was available, he was treated again with octreotide sc (200 μ g sc t.i.d) between October 1997 and February 1998. In this period, the nadir in total serum IGF-I concentrations in the pegvisomant-free period remained the same as before the first period of treatment with the GHR antagonist (around 150 nmol/L; see Table 1), indicating that he still was only partially sensitive to octreotide treatment.

From March 1998 onward, however, he was treated again with pegvisomant, without interruptions. In this period, pegvisomant was administered daily by sc injections, instead of weekly injections. A dose-responsive reduction in IGF-I was observed as daily doses were gradually increased from 10 mg sc to the maximal allowed daily dose in this study of 40 mg (see Fig. 1), although the final serum IGF-I concentration was still slightly above the upper limit of normal. This

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TABLE 1. Serum total IGF-I and tumor volume in cubic centimeters during medical treatment of a 34-yr-old acromegalic patient with octreotide alone, pegvisomant alone, and during coadministration with both compounds

Date	Pegvisomant dose	Octreotide dose	Volume (cc)	IGF-I (nmol/L)	Comments
July 1997	80 mg weekly		2.5	216	
October 1997		Octreotide 200 μ g t.i.d.	2.9	162	
March 1998	10 mg daily			152	
May 1998	10 mg daily		4.3	145	
June 1998	15 mg daily			127	
August 1998	20 mg daily			101	
October 1998	25 mg daily			140	
November 1998	30 mg daily			125	
February 1999	30 mg daily		4.9	80	
June 1999	35 mg daily			85	
July 1999	40 mg daily			102	
September 1999	40 mg daily		5.4	122	
October 1999	40 mg daily			103	Visual field defects
November 1999	40 mg daily	30 mg monthly (LAR)		82	Visual field defects
December 1999	40 mg daily	30 mg monthly (LAR)		35	Visual field defects
January 2000	40 mg daily	30 mg monthly (LAR)		37	Normalization of visual disturbances
March 2000	40 mg daily	30 mg monthly (LAR)	5.4	37	

resulted in high pegvisomant concentrations (concentrations around 50,000 ng/mL). Also, a very significant increase in serum GH levels was observed (maximal serum GH concentration during pegvisomant therapy, ~260 ng/mL).

During September and October 1999, serum total IGF-I concentrations started to increase again, while for the first time bitemporal visual fields defects were found because of a small, but significant, increase in tumor size, whereby the suprasellar extension was increased to the extent that compression of the chiasm was radiologically very likely (see Table 1). These observations were accompanied by an unexplained decrease in serum pegvisomant concentrations, without a change in dose. The patient's compliance was considered to be optimal throughout the whole period of observation, however (*e.g.* by the interpretation of drug-accountability forms).

In November 1999, it was decided to start treatment with octreotide, together with 40 mg sc pegvisomant once daily. Therefore, 30 mg Sandostatin LAR therapy was initiated. This resulted in a rapid normalization of serum total IGF-I concentrations within 2 months (see Fig. 1), whereas the abnormalities in the visual field completely resolved. Also, no further increase in tumor size on magnetic resonance imaging (MRI) was observed between July 1999 and March 2000. At the same time, a striking decrease in serum GH concentrations was observed as well, down to levels comparable with concentrations before the start of pegvisomant treatment. As least up to April 2000, serum IGF-I levels remained well controlled with levels around 35 nmol/L. Signs and symptoms of acromegaly were considerably improved as well.

Discussion

The primary goal in the management of acromegaly is to reverse the effects of GH hypersecretion and to decrease tumor size as much as possible (1–3). The importance of "normalizing" the GH/IGF-I axis has been demonstrated in two long-term studies of surgery (4, 5) in which the mortality rates of patients with acromegaly in whom disease control was inadequate were not different than those of matched controls, in contrast to the 2.4- to 4.8-fold greater mortality

in patients who had persistent disease. Therefore, tight control of the GH/IGF-I axis is now considered to be an achievable and desired goal of therapy (6).

The reported efficacy data of the available long-acting somatostatin analogs in reducing serum IGF-I levels in acromegalic patients indicate that effective control of disease activity can be achieved in two thirds of patients who are sensitive to somatostatin analogs (7–12). This leaves at least one third of the patients without an effective control of disease activity by medical intervention. To our knowledge, there are no reports available that describe an increase in size of a somatotropinoma during long-term treatment with somatostatin analogs.

The present case illustrates several important issues regarding the future use of GHR antagonists on a large scale in the (near) future.

Pegvisomant

Pegvisomant is a genetically manipulated GH molecule that disables functional dimerization of the two GHR molecules involved in signal transduction, due to a single mutation at the site II of the GH molecule. Pegvisomant is pegylated to increase serum half-life time and to reduce the likelihood of antibody formation. Currently, the compound is under investigation in the treatment of acromegaly (13–15). Pegvisomant blocks GH action, instead of inhibiting GH secretion as somatostatin analogs. This implies that during pegvisomant therapy GH levels are not indicative for GH-mediated action on IGF-I production. Although the unpegylated GHR antagonist does have a higher affinity at site I of the GH, compared with endogenous GH, one must conclude that the pegylation process has major influences on this affinity, because in this particular patient pegvisomant concentrations of as high as 50,000 ng/mL were not able to block GH action of GH concentrations more than 200-fold lower (250 ng/mL), although serum IGF-I concentrations in our patient nearly normalized when pegvisomant levels were around 50,000 ng/mL. Strikingly, in the Phase II and III studies, no clear-cut correlation between pegvisomant concentrations, GH levels, and efficacy data were observed (13–15). In this particular patient, pegvisomant concentrations

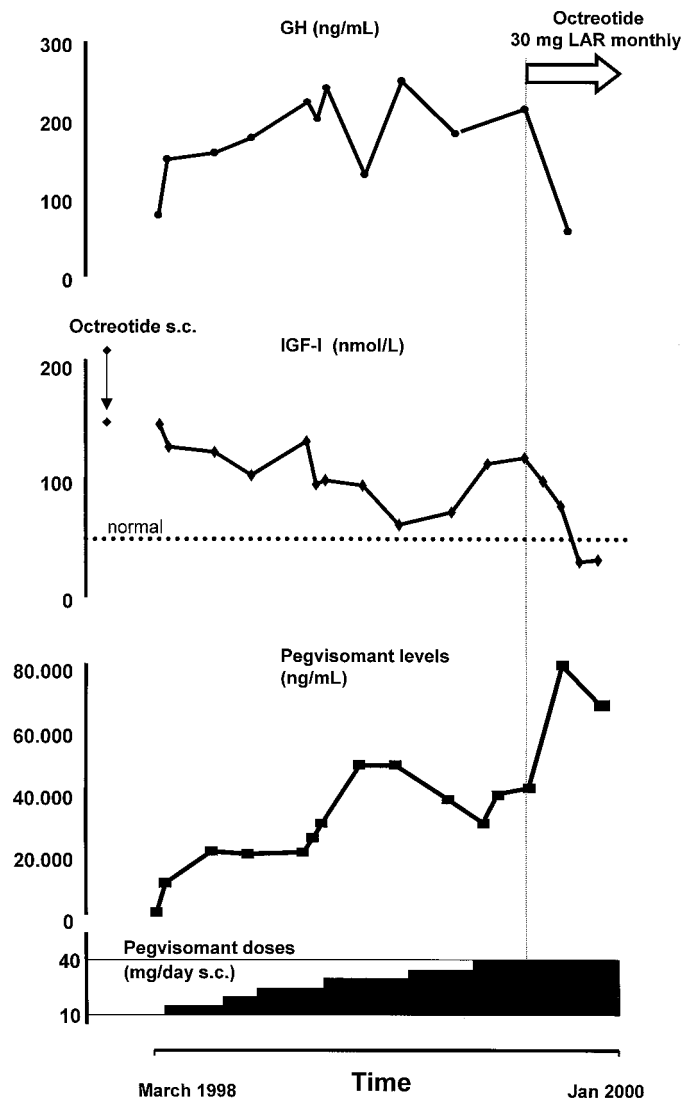


FIG. 1. Serum GH (ng/mL), serum total IGF-I (nmol/L), and serum pegvisomant (ng/mL) concentrations in an acromegalic patient during treatment with the GHR antagonist pegvisomant in increasing daily sc doses of 10–40 mg. The initiation of cotreatment with octreotide long-acting repeatable (30 mg monthly) is indicated by a dashed line. Middle, The initial decline in serum IGF-I concentrations during sc octreotide treatment (200 μ g t.i.d.) before the start of pegvisomant therapy is depicted as an arrow.

seem to be roughly correlated to the serum IGF-I response throughout the course of therapy. An unexpected finding was the 2-fold increase in serum pegvisomant concentrations, which was observed within 1 month after the initiation of octreotide treatment, while pegvisomant dosages were unchanged (40 mg daily). The reasons for this are unclear.

GH concentrations

As has been reported before, pegvisomant induces an increase in endogenous serum GH concentrations in acromegalic patients. Whether this dose-dependent increase in serum GH concentrations reflects a reduction in receptor-mediated GH clearance, an increase in production, or modification of some other pathway remains unclear yet.

Studies on the effect of GHR blockade on the pharmacodynamics of serum GH levels are currently being performed. The important observation in the present case, however, is that lowering serum GH concentrations by octreotide coadministration results in a synergistic decrease in serum IGF-I concentrations not achieved with octreotide or pegvisomant administered alone. This synergistic effect might be predicted, based on the mechanism of action of pegvisomant as a competitive GHR antagonist. Lowering GH levels would, therefore, make a given concentration of pegvisomant more effective.

Tumor size

The present case describes the first patient in whom progression in tumor size was encountered during treatment with pegvisomant. No data are yet available that indicate whether or not the size of a GH-producing tumor is modified by pegvisomant. It is, therefore, possible that some patients with aggressive tumors will show an increase in tumor size during long-term treatment with pegvisomant alone. Therefore, patients treated with pegvisomant should receive routine MRI monitoring of tumor size at least until more data become available. The aggressiveness of the tumor in this particular patient might reflect a subgroup of patients in whom a close follow-up of tumor size is mandatory with any treatment. It is still unclear, however, whether the observed increase in size of the tumor in this patient has been part of the natural history of growth of this tumor, in addition to growth secondary to the use of a GH antagonist. In this patient, cotreatment with octreotide and pegvisomant did result in an improvement in the visual field defects, whereas no further increase in tumor size was observed in between the last two MRI examinations 8 months apart. In this period, cotreatment was applied in the last 4 months.

Conclusion

We describe a 34-yr-old male acromegalic patient in whom a high dose of 40 mg pegvisomant (by sc daily injections) did not completely normalize serum IGF-I concentrations. Furthermore, he is the first patient in whom progression in tumor size was encountered during treatment with pegvisomant, and finally he was the first patient who was successfully treated with long-acting octreotide together with pegvisomant. This cotreatment resulted in an adequate control of biochemical disease activity, as well as an improvement of visual field defects and a further improvement in signs and symptoms.

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