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Growth Hormone Receptor Antagonist Therapy in Acromegalic Patients Resistant to Somatostatin Analogs

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ABSTRACT Transsphenoidal surgical resection is the primary therapy for acromegaly caused by GH secreting pituitary adenomas. Medical therapy for patients not controlled by surgery includes primarily somatostatin analogs and secondarily dopamine agonists, both of which inhibit pituitary growth hormone secretion. A novel GH receptor antagonist (pegvisomant) binds to hepatic GH receptors and inhibits peripheral insulin-like growth factor-1 generation. Six patients resistant to maximal doses of octreotide therapy received pegvisomant - three received placebo or pegvisomant 30 mg or 80 mg weekly for 6 weeks and three received placebo and pegvisomant 10-20 mg/d for 12 weeks. Thereafter, all patients received daily pegvisomant injections of doses determined by titrating IGF-1 levels. Serum total IGF-1 levels were normalized in all six acromegalic patients previously shown to be resistant to somatostatin analogs via a novel mechanism of peripheral GH receptor antagonism. The GH receptor antagonist is a useful treatment for patients harboring GH-secreting tumors who are resistant to octreotide.

Acromegaly, caused by GH secreting pituitary adenomas, has protean clinical and biochemical manifestations (1). Pituitary GH secretion is under hypothalamic GH releasing hormone and somatostatin control. These peptides bind to specific pituitary receptors and respectively stimulate and inhibit pituitary GH secretion (2). Circulating GH secreted by normal or adenomatous pituitary cells binds to hepatic GH receptors stimulating IGF-1 production from the liver and other tissues. GH hypersecretion in acromegaly results in elevated circulating IGF-1 levels. IGF-1 mediates several somatic and metabolic effects of GH (3) and contributes to cardiovascular, cerebrovascular, respiratory disease and possibly malignancy associated with acromegaly. There is a 2-4 fold higher mortality in acromegaly compared to the normal population and this increase has been primarily attributed to elevated GH levels (4,5).

As adverse mortality rates in acromegaly have been shown to approximate those of the normal population when GH is tightly controlled (4,5), the primary goal of therapy is normalization of elevated IGF-1 levels (6). Therapeutic modalities available to achieve this goal include transsphenoidal surgery, medical therapy and radiotherapy. Current medical therapies (short and long acting somatostain analogs and dopamine agonists) bind to pituitary receptors and inhibit pituitary adenoma GH hypersecretion. Dopamine agonists, including bromocriptine and long-acting cabergoline bind to pituitary dopamine type 2 receptors and control the GH-IGF-1 axis in less than 10% of patients receiving bromocriptine (7) but in up to 40% of patients receiving cabergoline. (8). Octreotide, an octapeptide analog of somatostatin, with similar affinity for the SSTR2 receptor is 45 times more potent than native somatostatin in its ability to inhibit pituitary GH release (9). Octreotide is administered either subcutaneously in divided doses of 100-500 mcg three times daily (10) or as a long acting depot analog administered intramuscularly monthly to suppress the GH-IGF-1 axis (11,13). Pegvisomant (B2036-PEG, Sensus Drug Development corporation, Austin, TX, is a novel, genetically-engineered analog of human GH which functions as a GH receptor antagonist and is administered as a daily subcutaneous injection in doses ranging from 10-30 mg/d. (14)

Octreotide normalizes IGF-1 levels in ~ 60% of acromegalic patients (12). Results of large long-term studies using longer acting depot somatostatin analogs are not yet available, however recently published short-term studies show that sandostatin LAR suppressed GH to less than 2.5ug/L in ~ 70% of patients (13), and lanreotide normalized IGF-1 in up to 60% of patients (11). Pegvisomant has been shown to normalize IGF-1 concentrations in 92% of acromegalic patients treated for up to 1 year (14). The present report describes six acromegalic patients who demonstrated no biochemical response to maximum doses of somatostatin analogs. All patients however, exhibited normal serum IGF-1 levels while receiving pegvisomant, a novel GH receptor antagonist.

PATIENTS AND METHODS

Six patients, aged 30-47 years, with biochemical confirmation of acromegaly and an IGF-1 of at least 1.3 times the upper limit of normal for age- and sex-matched controls were evaluated. Patients signed informed consent prior to enrolling in protocols approved by the Institutional Review Board. Octreotide therapy was discontinued at least 2 weeks and bromocriptine at least 5 weeks prior to screening evaluations. The first 3 patients were enrolled in a multicenter double blind parallel group study during which patients were centrally randomized to receive either placebo, 30 mg or 80 mg Pegvisomant once weekly by subcutaneous intra-abdominal injection for 6 weeks (14). After completion of the double blind phase, all patients received weekly subcutaneous injections of up to 80 mg pegvisomant weekly. Subsequently, daily dosing was instituted with a loading dose of 80 mg pegvisomant

followed by a 10 mg/d dose which was titrated up to 30 mg/d by 5 mg increments, based on IGF-1 levels.

Patients 4,5 and 6 were enrolled in a 12 week multicenter double blind placebo controlled study, receiving an 80 mg loading dose of pegvisomant followed by daily injections of either 10,15, or 20 mg or placebo. All patients then received a loading dose of 80 mg pegvisomant followed by 10 mg/day which was titrated by 5 mg increments to a potential maximal dose of 30 mg/day. The six octreotide-resistant patients analyzed here all eventually entered a study phase wherein the daily pegvisomant dosage was titrated depending on IGF-1 response.

ASSAYS

IGF-1 was measured by a competitive binding radiommunoassay (RIA) (Nichols Institute Diagnostics, San Juan Capistrano CA); free IGF-1 by a two-site immunoradiometric assay, using a kit from Diagnostic Systems Laboratory, Webster, TX. IGFBP-3 was measured by RIA (Endocrine Sciences, Calabasas Hills, CA). GH was measured by a commercial GH RIA modified to avoid cross-reactivity with pegvisomant (Endocrine Sciences, Calabasas Hills, CA). ALS was measured by RIA (Diagnostic Systems Laboratory Webster, TX)

RESULTS

The demographic and clinical characteristics of the 6 patients are presented in Table 1. All patients had previously undergone transsphenoidal pituitary surgery and 5 of 6 had received radiation therapy one to four years prior to the study. Each patient was previously receiving a maximal dose of somatostatin analog therapy (1200 mcg/d octreotide or lanreotide 30 mg weekly), which was discontinued at least 14 days prior to study entry and 5 of 6

Patient	Age	Sex	Time since Acromegaly diagnosis (years)	Tumor size	Previous treatment
1	30	F	6	macroadenoma with suprasellar extension and cavernous sinus invasion	surgery radiotherapy
2	32	M	3	macroadenoma with cavernous sinus extension	surgery radiotherapy
3	40	M	4	macroadenoma	surgery radiotherapy
4	31	M	5	macroadenoma	surgery radiotherapy
5	47	F	5	macroadenoma with cavernous sinus extension	surgery radiotherapy
6	45	F	2	macroadenoma with cavernous sinus extension	surgery

Table 1: Demographic data on patients.

had also received combination therapy with a dopamine agonist prior to pegvisomant therapy (table 2), with no response in serum IGF-1 levels. Patients were categorized as "resistant to octreotide" if IGF-1 levels either increased, remained unchanged, or decreased by less than ten percent on maximal doses of octreotide. Of the six patients described, IGF-1 levels increased in 3 patients, remained unchanged in one patient and decreased by ten percent in two patients receiving octreotide.

Fig 1 and 2 depict the IGF-1 responses to pegvisomant administration. In Fig 1, patients depicted were washed out from maximal doses of octreotide and parlodel which had failed to normalize IGF-1 levels. Patients received weekly pegvisomant therapy followed by incremental daily doses titrated according to IGF-1 levels. Patients 1,2 and 3 had unsuppressed mean IGF-1 levels of 872, 1147 and 600 ng/ml and GH levels of 39, 4 and 2 ng/ml on maximal doses of octreotide and parlodel. All three suppressed their IGF-1 levels into the normal range on 10 mg, 20mg and 10 mg respectively of daily pegvisomant injection. GH levels were 31 (n=19), 5 (n=16), and 4 (n=19) ng/ml respectively.

Fig 2 depicts persistently elevated IGF-1 levels in patients 4, 5 and 6 despite maximum doses of octreotide and dopamine agonist therapy. GH levels were 3, 4 and 38 ng/ml respectively. After a washout period, patients received placebo or 10, 15 or 20 mg pegvisomant injections daily followed by incremental daily pegvisomant doses up to 30 mg/d. All three patients normalized their IGF-1 levels when they were titrated to 25 mg/d pegvisomant. GH levels were 6.4 (n=11), 8 (n=7) and 111 (n=7) ng/ml respectively. No clinical or biochemical side effects or adverse effects of pegvisomant were documented during the time course of this study.

Patients	Medication	Maximum Dose	Mode of Delivery	Duration of Treatment
1	octreotide	1200 mcg/d	subcutaneous three times daily	Prior to surgery / radiotherapy and post operatively until study
	bromocriptine	10 mg qd	orally	Post surgery and radiotherapy
2	octreotide	1200 mcg/d	subcutaneous three times daily	post sugery and radiotherapy
	octreotide	720 mcg/d	continuous subcutaneous infusion	Discontinue subcutaneous octreotide and administer by continuous infusion for 2 months until study
	bromocriptine	15 mg/d	orally	post sugery and radiotherapy
3	octreotide	1200 mcg/d	subcutaneous three times daily	post radiotherapy until study
	bromocriptine	10 mg/d	orally	post radiotherapy
4	octreotide	1200 mcg/d	subcutaneously four times daily	octreotide started 1 year postoperatively, until study
	permax	0.05 mg	orally	permax started after radiotherapy
5	octreotide	1200 mcg/d	200 mcg subcutaneously 6 times daily	octreotide started 18 months after surgery, until study
	bromocriptine	10 mg/d	orally	Parlodel started two years after radiotherapy
6	lanreotide	30 mg	IM weekly	Four months, until study

Table 2: Prior somatostatin analog and dopamine agonist therapy in patients.

DISCUSSION

Current medical therapies for acromegaly (somatostatin analogs and dopamine agonists) reduce pituitary GH secretion by binding specific receptors on the tumor,

mimicking effects of physiological inhibitors of GH secretion. Somatostatin is synthesized as two bioactive peptides SRIF-14 and SRIF-28 (15) which have a high affinity for pituitary somatostatin receptors (16). Both peptides inhibit anterior pituitary GH secretion (17), after binding to one or more of five specific membrane receptors (16). These G-protein-coupled receptors, contain seven transmembrane domains and differ in their ability to inhibit adenylyl cyclase activity (16). About 10-15% of acromegalic patients however are non-responsive to somatostatin analogs, mostly due to a paucity of tumor somatostatin receptors (SSTR2) with a high affinity for octreotide (18,19). However, some tumors resistant to octreotide have been shown to bind somatostatin (18), suggesting heterogeneous expression of different somatostatin receptor subtypes in pituitary tumors (20). Octreotide and lanreotide bind with higher affinity to SSTR2 than to SSTR5 (21) which both facilitate inhibition of GH release by somatostatin (22).

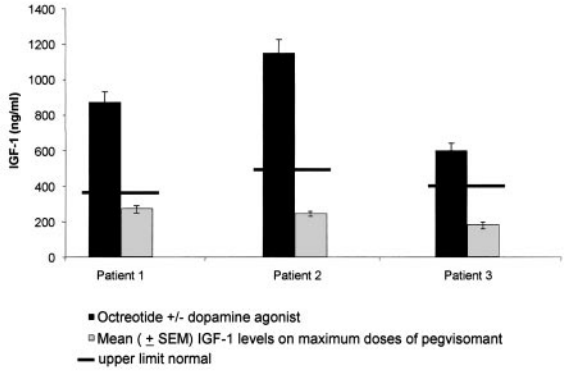

Fig 1: Mean ± SEM of serial IGF-1 levels in patients 1-3 on maximal dose of octreotide with or without dopamine agonist therapy and then receiving pegvisomant on a fixed dose weekly, weekly in incremental doses and then daily incremental doses titrated to IGF-1 (16-20 samples over 1 yr).

Whereas somatostatin analogs and dopamine agonists bind centrally to specific tumor receptors and inhibit pituitary GH secretion, pegvisomant acts at the peripheral GH receptor by blocking GH action. In the periphery, hGH has two binding sites for the extracellular domain of the GH receptor, the GH binding protein (GHBP) (23). Sequential binding of one GHBP molecule to site 1 on the GH molecule followed by binding to site 2 of a second GHBP results in two GHBP molecules bound to each GH molecule (23,24). Thus, ligand binding to the GH receptor is associated with subunit dimerization which triggers intracellular signaling resulting in IGF-I generation. Recombinant GH molecules mutated at sites 1 or 2, are unable to bind GHBP appropriately, preventing receptor dimerization, and subsequently, disrupt intracellular signaling and IGF-I generation. Pegvisomant, a GH analog with nine mutations (25) binds the receptor with increased affinity at site 1, and inhibits binding at site 2. Furthermore each molecule is covalently bound to 4-5 polyethylene glycol polymers which increase the biological half-life (25) and reduce antigenicity (26). Pegvisomant thus acts as a GH antagonist, by preventing appropriate receptor subunit dimerization thus blocking intracellular signaling with consequent abrogation of target tissue IGF-1 generation.

We describe 6 patients whose IGF-1 levels were totally unresponsive to maximum doses of somatostatin analogs, administered via different routes including SC thrice daily octreotide injections, continuous sc infusion and depot long-acting analog injection. Although their tumor sizes were unchanged, long-term impact on adenoma growth is unknown. GH levels increased in 5 patients, yet all of 6 patients demonstrated normalization of their

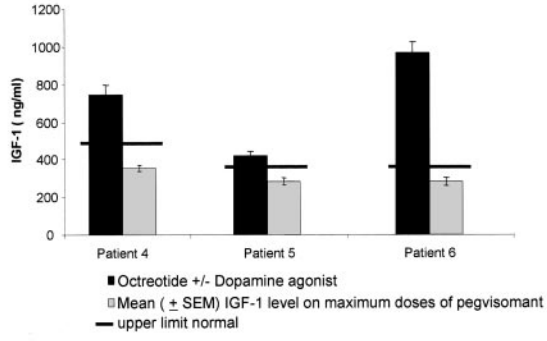

Fig 2: Mean ± SEM of serial IGF-1 levels in patients 4-6 on maximal doses of octreotide ± dopamine agonist, and then on pegvisomant administered in a fixed daily and then daily incremental doses titrated to the IGF-1 level (6-12 samples over 4 to 9 months).

IGF-1 levels while receiving pegvisomant, thus exhibiting, blocked peripheral GH action rather than GH secretion. Thus in these patients, Pegvisomant, by binding to hepatic GH receptors and inhibiting receptor dimerization appeared to block the subsequent GH signaling cascade culminating in IGF-1 secretion (27-30). As pegvisomant does not bind to GH secreting pituitary adenomas, tumor receptor characteristics which determine somatostatin analog efficacy, do not influence the efficacy of pegvisomant, which inhibits peripheral GH action, rather than secretion. It would be expected that despite normalized IGF-I levels, GH levels would remain elevated in these patients, albeit with minimal or neutralized peripheral bioactivity because of receptor blockade.

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