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Treatment of Pituitary Tumors

Pegvisomant

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Pegvisomant is a pegylated analog of growth that functions as a growth hormone receptor antagonist. The drug is capable of normalizing serum IGF-I concentrations (the chief mediator of disease activity in acromegaly) in 97% of patients, and therapy is associated with significant improvements in the symptoms and signs of GH excess. Biochemical control may be achieved with pegvisomant in patients wholly or partially resistant to somatostatin analogs, and there are emerging data to suggest that the drug may be particularly suitable for patients with acromegaly and co-existent diabetes mellitus.

Key Words: Pituitary tumors; pegvisomant; acromegaly; growth hormone (GH).

Introduction

Acromegaly is the condition caused by excess growth hormone (GH) secretion, usually from a pituitary somatotrope adenoma. Circulating GH interacts with cell-surface receptors to stimulate production of insulin-like growth factor-I (IGF-I), which is responsible for most of the signs and symptoms associated with the disease. Acromegaly is rare with new cases diagnosed at a rate of 4–6 per million per year and an overall prevalence of 40–60 per million. The diagnosis is confirmed by an elevated age-matched serum IGF-I level and failure of GH suppression to <1 μg/L following a 75 g oral glucose load. Treatment options include surgery, pituitary irradiation, and medical therapy. Surgery is often not curative, radiotherapy takes several years for its maximal effect, and, until recently, medical therapies have left a substantial proportion of patients with active disease. Pegvisomant (Somavert, Pfizer) is a new GH receptor antagonist, which has been developed for use in acromegaly. In this article, we describe the mechanism of action of pegvisomant, review some of the currently available clinical trial data, and discuss its potential role in the treatment of patients with acromegaly.

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Pegvisomant in Context

Transsphenoidal Surgery

Transsphenoidal selective pituitary adenomectomy remains the treatment of choice for most patients with acromegaly, being the only option to offer the prospect of "cure" with a rapid decline in GH levels. The goal is complete removal of all tumor, while simultaneously preserving or restoring normal pituitary function. Success rates vary between centers; curative outcomes of 61–91% are reported for microadenomas, and 23–53% for macroadenomas *(1–4)*. As 70% of patients have macroadenomas, the majority of patients are not cured by surgery.

Radiotherapy

External beam pituitary radiotherapy (RT) is frequently used in patients not cured by surgery and in those unfit or unwilling to undergo an operative procedure. Again, outcomes vary between centers; one study reported a normal serum IGF-I in 42% of patients approx 7 yr post-irradiation *(1)*. When longer time periods are employed, remission rates increase, with Biermasz et al. reporting a 75% remission rate after a mean follow-up of 11.6 yr *(5)*. All series report a high incidence of hypopituitarism *(1,5,20)*. Stereotactic (focused) radiotherapy (including proton beam, gamma-knife, and X-knife) allows higher doses of radiation to be delivered to a smaller target area. However, as these modalities are relatively new, their long-term efficacy remains to be seen, as does the incidence of hypopituitarism. For those patients in whom surgery is either not possible or non-curative, and who are awaiting the full effects of RT, medical therapy must be employed.

Medical Therapies

Dopamine Agonists

Dopamine agonists achieve useful reductions in GH and IGF-I, although only a minority of patients will achieve satisfactory disease control with this form of therapy alone. Normal serum IGF-I levels were achieved in 39% of patients overall with high dose cabergoline (up to 3.5 mg weekly); this value increased to 50% in patients whose tumors cosecreted prolactin with GH *(6)*. Side-effects such as gastrointestinal disturbance, postural hypotension, and lethargy are frequent and can be limiting. The benefit lies in their oral administration and relative inexpense.

Somatostatin Analogs

The majority of patients, however, have required somatostatin analogs, the gold standard to date. These are usually administered as depot monthly deep intramuscular injections, and octreotide (OCT-LAR) can normalize GH hypersecretion in 69% (≤2.5 μg/L), and IGF-I levels in 61% when administered for up to 24 mo *(7)*. By virtue of somatostatin receptors on the tumor itself, this class of drug has the added bonus of inducing tumor shrinkage, with the same study reporting that 53% of patients treated with OCT-LAR as primary therapy had a significant reduction in tumor volume (average of 50% after 12 mo), with two patients demonstrating complete resolution. This phenomenon has been described in other similar studies *(8–10)*.

Side-effects of somatostatin analogs include gastrointestinal upset (predominantly diarrhea and abdominal pain), development of gallstones and, in some patients, a deterioration in glucose tolerance *(11)*.

Although effective at controlling disease activity in the majority of patients, a substantial number have been left uncontrolled. The development of pegvisomant has provided a third option for this remaining group.

Pegvisomant

Pegvisomant is a GH receptor antagonist, which has been genetically engineered for use in acromegaly. GH is a 22-kDa, 191-residue peptide that binds two identical surface receptors to induce functional receptor dimerization, trigger secondary messengers, and generate IGF-I. Pegvisomant is a recombinant 191-amino-acid peptide that differs from GH by nine amino acids. Substitution of a glycine for arginine at a critical position for GH signal transduction and IGF-I synthesis prevents functional dimerization of GH receptors. Further amino acid substitutions give pegvisomant a kinetic advantage over endogenous GH. The peptide is pegylated (conjugation of polyethylene glycol moieties, mainly to lysine residues) to increase its circulating half-life and reduce its immunogenicity. Owing to its novel action blocking GH at the receptor site, GH can no longer be used as a marker of disease activity and, consequently, the goal is to reduce the serum IGF-I level into the age-related reference range.

Efficacy

Clinical studies have demonstrated this new medication to be the most effective form of medical therapy for acromegaly currently available. In a study of 112 patients with a serum IGF-I level at least 30% above the upper limit of normal range, dose-dependent reductions in serum IGF-I levels were evident in each of the treatment arms (10, 15, and 20 mg pegvisomant) compared with placebo. Normal IGF-I levels were achieved in 89% of patients receiving the 20 mg/d dose (Fig. 1). Parallel improvements in symptoms and soft tissue enlargement were also observed *(12)*.

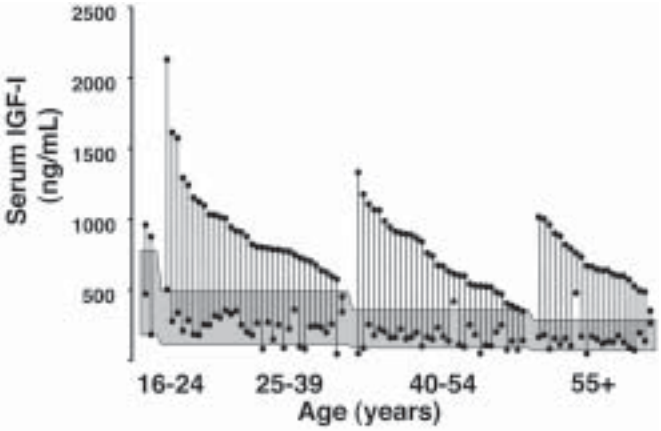

Fig. 1. Baseline and lowest values of individual serum IGF-I concentrations achieved in 90 patients treated for 12 months or more with daily pegvisomant. (Reproduced from van der Lely et al. *[13]*.) The shaded area represents the age-adjusted normal range for insulin-like growth factor-1.

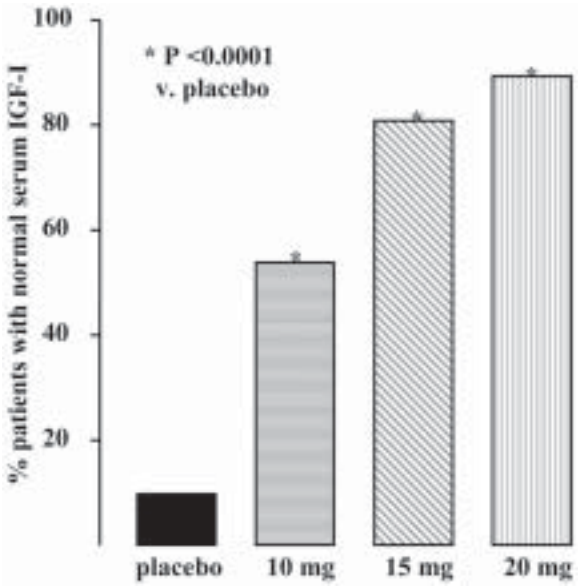

Fig. 2. Percentage of patients achieving normal age-related serum IGF-I values during 12 wk of pegvisomant therapy in the 10-, 15-, and 20-mg/d groups, respectively. (Adapted from Trainer et al. *[12]*.)

In a separate, open-label dose escalation study, results were even more impressive with 87 of 90 (97%) patients treated with doses up to 40 mg daily for a minimum of 12 mo achieving normal serum IGF-I concentrations (Fig. 2). The fall in IGF-I was accompanied by improvement in glucose tolerance and correction of several of the metabolic defects associated with acromegaly, such as cortisol, lipids, leptin, and bone (see below). Importantly, the drug works irrespective of previous responsiveness to somatostatin analog therapy *(21)*.

Side-effects

In studies thus far, pegvisomant has been well-tolerated with few side-effects. Significant hepatic transaminitis, re-

quiring discontinuation of therapy, was observed in two patients during clinical trials, with occasional similar, anecdotal, reports since then. The mechanism of this hepatotoxic effect is not clear; hepatotoxicity has not been reported with other pegylated compounds in clinical use [including pegylated interferon for the treatment of hepatitis C infection *(22)*] and no such adverse events have been evident in animal toxicology studies. Current recommendations are that tests of liver function should be performed 4–6 weekly for the first 6 mo of therapy or at any time in patients exhibiting symptoms suggestive of hepatitis.

Tumor Size

Pegvisomant does not act upon the tumor directly and makes no attempt to control GH levels. Hence, GH cannot serve as a tumor marker for patients with acromegaly treated with pegvisomant. For this reason, clinical trial protocols with pegvisomant have included regular detailed pituitary imaging by magnetic resonance. Two patients experienced clinically significant tumor growth during pegvisomant therapy necessitating further treatment *(13)*. Neither had received prior irradiation and both had large tumors on study entry. Overall, there is as yet no evidence that pegvisomant therapy is associated with an increase in tumor volume, but it is recommended that patients undergo regular surveillance imaging.

Metabolic Effects

Current consensus guidelines for remission of acromegaly include a GH nadir <1 μg/L following a glucose tolerance test and a normal serum age-matched IGF-I level. Given that pegvisomant works by blocking the action of GH rather than inhibiting its secretion, disease activity is solely monitored with serum IGF-I levels, rendering GH redundant as a tumor marker. Studies indicate that pegvisomant corrects many of the metabolic abnormalities accompanying acromegaly *(17,19)*, suggesting that restoring serum IGF-I to normal is an acceptable biochemical goal.

Insulin Sensitivity

GH has insulin antagonistic actions, leading to both ineffective suppression of hepatic glucose production and impaired glucose oxidation and uptake into peripheral tissues *(14)*. This is aggravated by the lipolytic action of GH, mobilizing free fatty acids (FFAs), which compete with glucose for uptake and oxidation *(15)*. In the long-term study reported by van der Lely et al. *(13)* pegvisomant administration for up to 18 mo induced a significant decrease in both fasting serum insulin and glucose concentrations in 160 patients. Clinically, this translates into reductions in insulin doses and cessation of oral hypglycemic agents in some patients *(16)*.

Cortisol Metabolism

Accelerated cortisol metabolism is a well-recognized feature of acromegaly and thought to be due to the action of GH on 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). This bidirectional GH-dependent enzyme is responsible for the interconversion of inactive cortisone and active cortisol; GH acts on 11β-HSD1 to favor cortisone formation, thereby effectively increasing cortisol clearance *(18)*. Studies indicate that pegvisomant inhibits this action, and returns cortisol metabolism to normal *(19)*.

GH Levels

To achieve effective antagonism plasma concentrations of pegvisomant, approx 1000-fold greater than GH levels are required. Together with the high degree of homology between pegvisomant and GH, measuring GH in the presence of pegvisomant is not straightforward and has required the development of a dedicated assay specific for GH. In the open-label dose escalation study, GH levels rose by as much as 14.2 μg/L (76.0%) within 2 wk of commencing therapy, mirroring the fall in IGF-I; following this initial rise, levels appear to plateau with no further increases seen with chronic therapy. The significance of this rise, in the presence of effective GH antagonism, is not clear.

Pegvisomant in the Acromegaly Treatment Algorithm

For most patients with acromegaly, transsphenoidal surgery will remain the treatment of choice, offering the prospect of permanent cure. However, given that most patients have macroadenomas, many patients will require adjunctive therapy following non-curative surgery. The place of radiotherapy in the treatment of acromegaly is still evolving and data regarding long-term effects of newer stereotactic radiotherapy are awaited. Medical management options have changed substantially in recent years, with the development of depot preparations of somatostatin analogs and pegvisomant. Because of their oral administration and relative inexpense, many patients (particularly those with mixed GH/prolactin secretion and those with less severe GH excess) merit a trial of dopamine agonist therapy. For most patients requiring medical therapy, somatostatin analogs remain the "gold standard."

Pegvisomant is currently indicated for the treatment of patients with acromegaly who have had inadequate response to surgery and/or radiotherapy and in whom an appropriate medical treatment with somatostatin analogs was not tolerated or did not normalize IGF-I concentrations. Preliminary data suggest that pegvisomant may be a particularly suitable therapy for patients with acromegaly and associated impaired glucose tolerance/diabetes.

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