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Pegvisomant

Treatment of Acromegaly
Growth Hormone Receptor Antagonist

B2036-PEG
G120K-PEG
Somavert™
Trovert™

Pegylated human growth hormone mutein

EN: 253947

Introduction

Growth hormone (GH, somatotropin), a peptide hormone secreted from the anterior pituitary, is particularly important for normal growth and development. Secretion of GH is stimulated by the growth hormone-releasing hormone (GHRH) and inhibited by somatostatin. The interaction of these hormones regulates the secretion of GH. Secretion of GH by the pituitary into the bloodstream produces insulin-like growth factor-1 (IGF-1, somatomedin C) in the liver. Many effects of GH on promoting growth of bone and other tissues in the body are mediated by IGF-1.

Acromegaly is a hormonal disorder that is caused by prolonged overproduction of GH by the pituitary gland in middle-aged adults. In over 90% of acromegaly patients, excess of growth hormone is associated with a benign tumor of the pituitary (adenoma). If overproduction of GH occurs during childhood and prior to epiphyseal fusion, a proportional skeletal growth is produced leading to gigantism.

Although small pituitary adenomas are quite common (found in up to 20% of the U.S. population during autopsy), the prevalence of the disease is relatively low (40-60 per million). About 3 out of every million people in the U.S. develop acromegaly each year (1).

Current treatment options of acromegaly include surgical removal of the tumor, radiation therapy of the pituitary and pharmacologic treatment (2-4).

Pharmacological reduction of GH levels can be achieved using dopamine agonists or somatostatin analogs, although most evidence suggests that somatostatin analogs are more effective than dopamine agonists. In selected patients, dopamine agonists such as bromocriptine mesylate (Parlodel®, Novartis) are initially preferred because they can be taken orally. However, a decline in GH and IGF-1 levels and a reduction in tumor size are only achieved in less than half of the patients using these drugs. Side effects of dopamine agonists are mainly gastrointestinal and include nausea and vomiting (5).

Somatostatin analogs have been shown to be effective for long-term treatment and reduce GH levels in most patients and normalize IGF-1 levels in 60-65% of patients. Reduction in tumor size with these drugs is only attained in 40% of patients (6). Octreotide (Sandostatin®, Novartis) and its long-acting injectable suspension formulation, Sandostatin LAR®, are the only somatostatin analogs approved in the U.S. as a treatment for acromegaly. Lanreotide acetate (Somatuline LP®, Ipsen) is another octapeptide somatostatin analog that has been approved in some European countries. Somatostatin analogs have a longer duration of action compared to somatostatin and are more potent and selective inhibitors of GH release. BIM-23190 and BIM-23197 (Biomeasure) are new somatostatin analogs under preclinical investigation that have demonstrated improved stability and distribution characteristics (7).

Side effects of somatostatin analogs are related to their inhibitory action on gastrointestinal motility and may include loose stools, diarrhea, nausea, malabsorption and flatulence (8). Approximately 20-30% of patients develop gallstones or sludge, which are usually asymptomatic (9).

The GH receptor antagonists, including the title compound, are a new class of drugs with potential usefulness in the pharmacological management of human GH-related pathologies including acromegaly.

Pharmacological Actions

Pegvisomant, a competitive GH receptor antagonist, is a PEGylated form of B2036, a recombinant human GH antagonist. It contains eight amino acids mutated at site

X. Rabasseda, P. Leeson. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

1, which increases its affinity for GH-binding protein, and one amino acid mutated at site 2 (G120K), which prevents receptor dimerization and provides the basis for its antagonist activity. The pegylation of the GH analog offers a longer biological half-life. It has been shown in vitro to completely block GH stimulation of the STAT5 reporter constrict. It has 5 times higher affinity for human GH than for GH-binding protein, and is internalized rapidly with a time course similar to that of the human hormone (10).

Receptor trafficking after treatment with human GH or pegvisomant was studied in HEK293 human epithelial kidney cells, which physiologically express GH receptor. Both GH and the GH antagonist were rapidly internalized after treatment (11).

GH therapy increases hepatic, skeletal and epiphyseal IGF-1 secretion, which circulates mainly bound to IGF-binding protein-3 (IGFBP-3). Furthermore, like IGF-1, IGFBP-3 synthesis and release are also dependent upon GH. IGFBP-3 production and release are also induced by IGF-1, at least in some animals. Estradiol has an additional facilitating effect on IGF-1 and IGFBP-3 production and release through the induction of GH secretion. Pegvisomant has been shown to normalize diabetic renal and glomerular hypertrophy after 1 month of treatment (2 mg/kg s.c. every other day) in streptozotocin-diabetic mice. The drug also reduced diabetes-associated urinary albumin excretion, but did not affect metabolic control of blood levels of GH, IGF-1 or IFGBP-3, indicating that its effects may be mediated by specific inhibition of renal IGF-1 through the renal GH receptor.

Both GH and IGF-1 are involved in the development of renal complications of diabetes mellitus. In a placebo-controlled study, pegvisomant was administered subcutaneously every other day for 28 days to normal and streptozotocin-induced diabetic mice and its effects on renal/glomerular hypertrophy and urinary albumin excretion (UAE) were evaluated. Placebo-treated diabetic mice suffered growth retardation, hyperphagia, hyperglycemia, renal/glomerular hypertrophy, increased serum GH levels, increased UAE and decreased serum IGF-1, IGFBP-3 and liver IGF-1 levels. Diabetic mice treated with pegvisomant, in contrast, had normal kidney IGF-1 levels, normal kidney weight and glomerular volume and a less significant increase in UAE. Thus, the drug appeared to be effective in specifically limiting the renal effects of diabetes in mice while not affecting metabolic control or circulating levels of IGF-1, GH or IGFBP-3. These renal effects of pegvisomant, therefore, probably stem from the direct inhibition of renal IGF-1 via the renal GH receptor. Based on these findings, specific renal GH receptor blockade has been suggested as a novel concept in the treatment of diabetic kidney disease (12, 13).

The modulating effect of estrogens on GH and the increased incidence of breast cancer and meningiomas in patients with acromegaly led to the investigation of the effect of pegvisomant on these malignant neoplasms in animal models. In nude mice bearing breast cancer xenofrafts, pegvisomant (202.5 mg/kg/week in 3 divided doses) significantly reduced the volume of T-47D and MCF-7 xenografts, two estrogen receptor-negative cell lines. It also tended to reduce tumor volume in ZR-75-1 and MDA-MB-231 xenografts, estrogen receptor-positive and -negative cells, respectively (14). Similarly, pegvisomant was found to significantly reduce meningioma growth in xenografted nude mice (15).

Human GH is able to activate prolactin receptor, as well as its own receptor. However, data from studies in rat Nb2 cells rule out any effect of pegvisomant on prolactin receptor, emphasizing the high selectivity of this analog (16).

Pharmacokinetics and Metabolism

A sensitive radioimmunoassay for the quantification of pegvisomant using rabbit antibodies has been selected that allows meaningful determinations of its pharmacokinetics (17).

The pharmacokinetics of pegvisomant administered as single rising doses of 0.03-1.0 mg/kg s.c. were assessed in healthy volunteers and patients with acromegaly in 2 studies (Table I). C_{max}, t_{max} and AUC values increased with dose, with values of 0.09-9.6 μg/ml, 15-77 h and 9.3-1594 μg·h/ml, respectively. The terminal elimination $t_{1/2}$ was similar in all dosing groups, although differences were noted between the two studies (18, 19).

Clinical Studies

In healthy volunteers, pegvisomant blocked GH-induced increase in IGF-1 levels but had no effect on GH production, indicating that the compound has a potential therapeutic role in refractory acromegaly (20) (Box 1).

Pegvisomant is currently in phase III clinical studies as an antidiabetic and as a treatment for acromegaly. It may also prove useful for the treatment of diabetic kidney disease. The safety and pharmacodynamics of pegvisomant were assessed in 36 healthy volunteers administered single rising doses (0.03, 0.1, 0.3 and 1.0 mg/kg s.c.) in a double-blind, placebo-controlled design. The drug was well tolerated at all doses and significantly suppressed IGF-1 levels at a dose of 0.3 mg/kg in 3/6 subjects and at 1.0 mg/kg in 6/6 subjects (18).

Subsequently, daily use of pegvisomant (10-20 mg s.c.) in 7 patients with acromegaly resulted in significant decreases in IGF-1 and IGFBP-3 levels, with normalization in 6 patients. The treatment was well tolerated (21) (Box 2).

The efficacy and tolerability of pegvisomant in the treatment of acromegaly were demonstrated in a multicenter, randomized, placebo-controlled, double-blind phase II study in 46 patients. Patients were treated with 30 or 80 mg/week for 6 weeks and then, in an open extension phase of 5.4 and 5.9 months, with weekly and daily treatment at 10-30 mg/day, respectively. Serum IGF-1 levels decreased by a mean of 16% and 31% on the low and high doses, respectively, although normal

Table I: Pharmacokinetic properties of pegvisomant administered s.c. single doses to healthy volunteers and patients with acromegaly (18, 19). [Prous Science PKline® database].

Parameter	Healthy volunteers				Acromegalic subjects	
	0.03 mg/kg	0.1 mg/kg	0.3 mg/kg	1 mg/kg	0.3 mg/kg	1 mg/kg
C_{max} (ng/l)	0.1	0.5	1.9	9.6	1.8	6.5
t_{max} (h)	15	36	38	60	33	77
AUC (ng·h/l)	9.3	39.4	193	1590	234	1060
$t_{1/2}$ (h)	77.1	83.5	61.2	74.2	109	80

Box 1: Effect of pegvisomant in healthy volunteers (20) [Prous Science CSline database).

Design	Placebo-controlled, dose-finding clinical study
Population	Healthy male volunteers aged 18-37 years (n = 36)
Treatments	Pegvisomant (P), 0.03 mg/kg s.c. (n = 6) P, 0.1 mg/kg s.c. (n = 6) P, 0.3 mg/kg s.c. (n = 6) P, 1 mg/kg s.c. (n = 6) Placebo (Pl) (n = 12)
Adverse Events	All doses of pegvisomant were well tolerated
Results	IGF-1 levels, 5% change: P1* (–49) > P0.3* (-28) > Pl [*p <0.001] Serum GH levels did not change
Conclusions	Pegvisomant blocked peripheral GH activity without enhancing its secretion

Box 2: Effect of pegvisomant in patients with acromegaly (21) [Prous Science CSline database].

Design	Open clinical study
Population	Patients mean age 58 years (n = 7)
Treatments	Pegvisomant, 10 mg/d s.c. x 2 wks → 15 mg s.c. x 2 wks → 20 mg/d s.c. with monthly review
Adverse Events	No significant side effects were reported
Results	IGF-1 levels (ng/ml), change: –665; normalization rate: 85.7% IGFBP-3 levels (mg/l), change: –2; normalization rate: 85.7%
Conclusions	Pegvisomant was highly effective in the treatment of acromegaly with no adverse events or evidence of pituitary tumor growth

serum IGF-1 levels were obtained in only 1/16 and 3/15 patients in each respective dose group. At the end of the 6-week blinded study, patients were continued in an open-label, dose-titration phase and all received active drug (10-30 mg/day). Daily treatment at the time of reporting had continued for a mean of 8.8 months, with mean decreases in serum IGF-1 levels of 69% and the normal age-related range obtained in 92% of all pegvisomant-treated patients. Cortisol metabolism was normalized as a result of GH inhibition by the drug, indicating that cortisol clearance rates are accelerated in patients with active acromegaly. Again, the drug was reported to be well tolerated, with no significant side effects or evidence of pituitary tumor growth (22-24) (Box 3).

During the daily dosing extension of the above study, serum levels of acid labile subunit of GH were found to correlate more strongly than other GH axis indices. Reductions from 2462 to 2264 mU/ml in the 30-mg pegvisomant group and from 2388 to 1833 mU/ml in the 80-mg group were seen in the randomized, placebo-controlled phase. Further reductions to 1763 mU/ml after the open-label weekly dosing and to 1318 mU/ml after the open-label daily dosing were obtained (the normal values for adults were in the range of 559-1550 mU/ml) (25) (Box 4).

Similar results of efficacy and tolerability were documented in the interim analysis of a clinical study including 116 patients from 16 centers in the U.S. and Europe designed to evaluate the safety and efficacy of

Box 3: Efficacy and tolerability of pegvisomant in patients with acromegaly (22-24) [Prous Science CSline database].

Design	Multicenter, randomized, double-blind, placebo-controlled clinical study
Population	Patients mean age 47 years (n = 46)
Treatments	Pegvisomant (P), 30 or 80 mg/wk s.c. x 6 wks → 30-80 mg/wk x 5.4 months (mean) → 10-30 mg/d x 5.9 months (mean) Placebo (Pl) x 6 wks → Pegvisomant, 30-80 mg/wk x 5.4 months (mean) → 10-30 mg/d x 5.9 months (mean)
Results	GH levels (µg/l), change at 6 wk/8.1 months/10.8 months: 1/–3/5 IGF-1 levels (ng/ml), change at 6 wk/8.1 months/10.8 months: –151/–395/–574 Normalization rate at 6 wk: P30 (1/16 [6.3%]) < P80 (3/15 [20.0%]) IGFBP-3 levels (mg/l), change at 6 wk/8.1 months/10.8 months: –0.4/–0.9/–1.7 No changes in pituitary magnetic resonance imaging
Conclusions	Pegvisomant was effective in reducing IGF-1 levels in this study population

Box 4: Effect of pegvisomant on acid labile subunit levels in acromegaly (25) [Prous Science CSline database].

Design	Randomized, placebo-controlled, double-blind clinical study
Population	Patients with acromegaly (n = 38)
Treatments	Pegvisomant (P), 30 or 80 mg/wk s.c. x 6 wks → 30-80 mg/wk x 5.4 months (mean) → 10-30 mg/d x 5.9 months (mean) Placebo (Pl) x 6 wk → Pegvisomant, 30-80 mg/wk x 5.4 months (mean) → 10-30 mg/d x 5.9 months (mean)
Results	Acid labile subunit levels (mU/ml) at 6 wk: Pl (no change) < P30 (–198) < P80 (–555); at 6.9/12.8 months: –662/–1107; at study end: 1318 [normal range: 550-1550]
Conclusions	Pegvisomant effectively reduced acid labile subunit, an excellent tool for monitoring the therapeutic effect in the treatment of acromegaly

pegvisomant in patients with acromegaly. Patients were randomized to treatment with pegvisomant 10, 15 or 20 mg/day s.c. for 12 weeks. Significant reductions in IGF-1 as well as relief of clinical symptoms were seen; reduction in IGF-1 was significant across all 3 active dose groups and reached 89% in the 20 mg/day group. Pegvisomant was well tolerated and was effective even in patients previously considered to be refractory to medical therapy (26).

In a clinical study designed to assess insulin resistance in 3 patients (aged 28-55 years) with acromegaly, treatment with pegvisomant for 13 months at doses adequate to normalize IGF-1 levels effectively improved insulin resistance by antagonizing the GH receptor. As no changes in diet or exercise were included in the study protocol, the effect of pegvisomant was assumed to be independent of weight (27).

Pegvisomant received Orphan Drug status from the U.S. FDA in 1997 for the treatment of acromegaly (28).

Manufacturer

Sensus Drug Development Corp. (US); licensed from Genentech, Inc. (US).

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