CLINICAL STUDY

Successful treatment of resistant acromegaly with a growth hormone receptor antagonist

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Abstract

Background/objective: Pegvisomant is a pegylated analogue of human GH and functions as a potent GH receptor antagonist. This novel mode of action gives it the potential to achieve biochemical control in patients with acromegaly whose disease activity cannot be satisfactorily controlled by conventional therapy. We have documented the clinical details of seven patients with residual active acromegaly after surgery and/or radiation therapy successfully treated with pegvisomant.

Patients/methods: Seven patients (four male, mean age 47 years, range 34–67 years) who participated in two separate clinical trials of pegvisomant have completed 2 years (four patients) or 1 year (three patients) of treatment. All had active acromegaly (mean serum GH level >5 mU/l; serum IGF-I elevated for age) that could not be controlled with standard medical therapy (dopamine agonist and/or a somatostatin analogue) following appropriate primary treatment with surgery and/or radiotherapy.

Results: On a median dose of 20 mg/day (range 15–40) pegvisomant, serum IGF-I fell from a mean of 920 ± 351 ng/ml (s.d.) to 258 ± 91 ng/ml and was normalised in all seven patients. These changes were associated with improvements in soft tissue enlargement and general well being. Treatment was well tolerated and no change in pituitary tumour size was evident on MRI scans performed every 6 months.

Conclusions: Treatment with pegvisomant is safe and efficacy is maintained after 2 years. Serum IGF-I may be normalised in patients who are refractory to conventional therapy.

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Introduction

Conventional treatment options for patients with acromegaly consequent upon a pituitary adenoma include surgery (usually via the trans-sphenoidal route), external pituitary irradiation and medical therapy. Trans-sphenoidal adenomectomy will result in cure in 60–90% of patients if the pituitary tumour is a microadenoma (1, 2), but this figure falls to <50% for larger lesions that extend outside the pituitary fossa (3, 4). External beam pituitary radiotherapy is an effective method of preventing tumour recurrence and arresting tumour growth but works slowly (5, 6). Options for medical therapy currently include dopamine agonists (such as bromocriptine or cabergoline) and synthetic analogues of somatostatin (SST), namely octreotide and lanreotide, either as short-acting or depot, slow-release formulations. Bromocriptine lowers mean serum growth hormone (GH) to the 'safe' range in <20% of patients (7, 8). A higher response rate is seen with the longer acting dopamine agonist cabergoline; around 50% of patients with a pretreatment serum insulin-like

growth factor-I (IGF-I) level ≤ 750 ng/ml will achieve a serum IGF-I level ≤ 300 ng/ml compared with 17% with a pretreatment level ≥ 750 ng/ml (9). Between 45 and 65% of patients will achieve satisfactory biochemical control on octreotide, either in short-acting or depot preparations (10–13).

Pegvisomant (Sensus Drug Development Corporation, Austin, TX, USA) is a novel, genetically engineered analogue of human GH that functions as a GH receptor antagonist (14, 15). In a recent study, it was shown to be an effective treatment for patients with acromegaly, capable of lowering circulating IGF-I levels to normal in 89% of patients at a dose of 20 mg daily (16). It therefore has the potential to achieve biochemical control in patients whose disease activity cannot be satisfactorily controlled with conventional therapy. We report here its successful use to treat seven patients with persistent acromegaly, in whom adequate symptomatic and biochemical control could not be otherwise achieved following treatment with surgery and/or radiotherapy and conventional medical therapy with octreotide and/or dopamine agonists.

Subjects and methods

Patients

Seven patients (four male, mean age 47 years, range 34–67 years) were studied. Details of previous therapy for acromegaly and details of serum GH and IGF-I values are given in Table 1. All patients had symptomatic and biochemical active acromegaly (mean GH >5 mU/l obtained from five samples obtained over 12 h; serum IGF-I above the age-related reference range) despite standard doses of a dopamine agonist and/or an SST analogue. Four of the patients were originally enrolled into a 6-week, double-blind placebo-controlled trial of weekly pegvisomant injections in July 1997 (17). At the conclusion of the study, all four continued into an open-limb study of escalating doses of weekly pegvisomant, up to a maximum of 80 mg weekly. After 6 months, treatment was switched to daily dosing, initially at a dose of 10 mg per day, increasing by 5 mg per day every 2 weeks if the serum IGF-I level remained above the upper limit of the age-related reference range, to a maximum of 40 mg daily. Two patients were enrolled into a separate, 12-week, double-blind placebo-controlled trial of daily pegvisomant in July 1998; treatment was then continued into an open-limb study. Data from these two patients were included in a recent report of the efficacy of pegvisomant in the treatment of acromegaly (16). A further patient entered the open-label extension of the second placebo-controlled study on compassionate grounds. None of the patients had received a long-acting SST analogue within 12 weeks of commencing pegvisomant. Pituitary hormone deficiencies were appropriately replaced with thyroxine, hydrocortisone, gonadal steroids or desmopressin as needed.

Study protocol

All patients gave written informed consent and were told of their right to discontinue treatment at any time. The study protocols were approved by the Ethics Committees of the East London and City Health Authority, London, UK and South Manchester Hospitals, UK. Patients taking short-acting octreotide and/or dopamine agonists discontinued this therapy for 2 or 5 weeks respectively (drug 'washout' period). Patients were eligible for the study if the serum IGF-I level after the washout period was 30% above the upper limit of the age-related reference range (see Table 1).

Treatment

A lyophilised powder of pegvisomant was reconstituted with 1 ml water for injection and self administered as a single, daily subcutaneous injection.

Measurements

The primary efficacy endpoint used was normalisation of serum IGF-I, measured by radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA).

Magnetic resonance imaging (MRI) scans

All patients underwent MRI of the pituitary using a standard protocol, with and without gadolinium contrast enhancement, at the start and completion of the respective placebo-controlled study and, subsequently, at 6-monthly intervals.

Results

Serum IGF-I levels

Mean serum IGF-I off all treatment immediately prior to commencing pegvisomant was 920 ± 351 ng/ml (s.d.). Serum IGF-I after 2 years of therapy (patients 1–4) and after 1 year of therapy (patients 5–7) was 258 ± 91 ng/ml (s.d.) on a median dose of pegvisomant of 20 mg daily (range 10–40) (Table 2). In all cases, serum IGF-I fell to within the age-related reference range during therapy with pegvisomant (Fig. 1).

Adverse events

Treatment with pegvisomant was well tolerated and no patient withdrew from the study. No patient reported an injection site reaction. In one patient a diagnosis of temporal lobe epilepsy was made. Symptoms were present prior to starting pegvisomant and have since been abolished, during treatment with pegvisomant, by sodium valproate (800 mg twice daily). In another patient, transient asymptomatic elevation of hepatic transaminases was noted (peak aspartate aminotransferase (AST) 80 IU/l, normal 15–35). Therapy was not interrupted, no other laboratory abnormalities were noted and the level returned to normal after 4 weeks. There has been no evidence of tumour growth on MRI in any of the seven patients.

Discussion

All currently available therapies for acromegaly aim to reduce GH secretion by the pituitary tumour, with consequent lowering of serum GH and IGF-I concentrations. The chances of a surgical 'cure' for acromegaly are considerably greater for microadenomas compared with those with a diameter >1 cm (1, 2, 18). Surgical experience and expertise is also a defining variable, with outcomes differing greatly between centres (19). External beam radiotherapy (EBRT) is a well-established therapy for patients not

Figure 1 Baseline and most recent serum IGF-I levels in seven octreotide-resistant patients treated with pegvisomant.

cured by surgery or unfit/unwilling to undergo an operation. Most reports of the effectiveness of EBRT in the treatment of acromegaly have used serum GH concentration as the marker of therapeutic efficacy and indicate, in general, a 50% reduction during the first 1–2 years after EBRT, declining further to 25% of the pre-radiotherapy level by 5 years (5, 20, 21). The chances of achieving 'safe' GH levels following EBRT depend largely on the pre-EBRT GH level, with the probability of success significantly greater in patients with pre-EBRT values of 30 mU/l compared with those with GH levels >30 mU/l (22). Long-term data regarding the effectiveness of focussed EBRT, using either a linear accelerator or a gamma knife, are not yet available.

Standard medical therapies for acromegaly include dopamine agonists and SST analogues. Bromocriptine causes some reduction of GH levels in the majority of patients, but 'safe' levels are achieved in <20% (7, 8). This figure is higher with the longer acting dopamine agonist cabergoline, although satisfactory biochemical control is achieved in <50% of patients overall (9). As with surgery and EBRT, the chances of achieving satisfactory biochemical control with cabergoline are largely dictated by the pretreatment serum GH/IGF-I values, with normal levels achieved in only 17% of patients with pretreatment serum IGF-I levels of 750 ng/ml (9). SST analogues, such as octreotide or

lanreotide, reduce GH secretion in acromegaly by binding to one or more of five G protein-coupled SST receptors (23). Therapy with SST analogues, either short-acting or in depot formulation, is associated with 'safe' GH levels in 45–65% of cases (10–13), but there remains an important group of patients whose disease cannot be satisfactorily controlled with this modality of therapy. This, in turn, is presumably either because some somatotroph pituitary adenomas express few or no SST receptors (most notably type 2 receptors) (24) and/or that those receptors are not functionally linked to GH secretion (24, 25). In patients whose tumours express SST receptors, the pretreatment serum GH/IGF-I levels are an important determinant of the likelihood of achieving satisfactory biochemical control; patients with more severe biochemical disease are likely to require higher doses of SST analogues, but increasing the dose above 600 µg/24 h (short acting) or 30 mg/month (depot) octreotide is unlikely to result in significant further benefit (10, 11, 13). An increased knowledge of the pharmacology of the SST receptor family may lead to the design of more efficacious synthetic analogues, but is unlikely to significantly affect the outlook for patients whose tumour is unresponsive to currently available somatostatinergic therapies.

Pegvisomant is a genetically engineered analogue of human GH (14, 15). Its amino acid sequence, with

Table 1 Details of previous therapies and doses and serum GH/IGF-I values in seven octreotide-resistant patients treated with pegvisomant (Peg)

Patient no.	Sex	Age (years)	Mean GH at diagnosis (mU/l)	Surgery (year and route)	Radiotherapy dose (type, year)	Treated pituitary hormone deficiencies	Lowest mean GH prior to Peg (mU/l)	Lowest IGF-I prior to Peg (ng/ml) (age-adjusted range)	Therapy on which lowest mean GH and IGF-I achieved
1	F	41	300	1978 (TSS)	4500 cGy (EBRT, 1977)	ACTH, TSH	320	1087 (126–369)	OT 2500 µg/day
2	M	43	190	1987 (TFS)	2000 cGy (γknife, 1989)	FSH/LH	65	900 (126–369)	OT 600 µg tds
3	M	34	150	1981 (TFS)	4000 cGy (EBRT, 1982)	ACTH, TSH, FSH/LH, ADH	53	711 (114–492)	LAR 30 mg/4 weekly
4	M	43	110	1996 (TSS)	4500 cGy (EBRT, 1995)	None	21	641 (126–369)	BC 10 mg
5	F	46	200	1996 (TSS)	4000 cGy (EBRT, 1988)	ACTH, TSH, FSH/LH	12	417 (126–369)	OT 100 µg tds
6	F	55	32	1988 (TSS)	4000 cGy (EBRT, 1988)	FSH/LH	13	374 (108–263)	Cab 0.5 mg 3×/week
7	M	67	30	1993 (TSS)	4500 cGy (EBRT, 1993)	ACTH, TSH, FSH/LH	8	349 (108–229)	LAR 30 mg/4 weekly
				1997 (TFS)	2000 cGy (SMART, 1996)	FSH/LH			OT 600 µg tds
				None	4500 cGy (EBRT, 1985)	ACTH, TSH, FSH/LH			OT 600 µg tds

EBRT = external beam pituitary irradiation, TSS = trans-sphenoidal surgery, TFS = trans-frontal surgery, SMART = stereotactic multi-arc radiotherapy, OT = octreotide (short acting), LAR = slow release (depot) octreotide, BC = bromocriptine, Cab = cabergoline, ACTH = adrenocorticotrophin, TSH = thyrotrophin, FSH = follicle-stimulating hormone, LH = luteinizing hormone, ADH = antidiuretic hormone, tds = three times daily.

Table 2 Serum IGF-I values before and during treatment with pegvisomant (Peg), plasma pegvisomant concentrations and serum GH concentrations in seven octreotide-resistant patients treated with pegvisomant.

Patient no.	IGF-I prior to Peg (ng/ml) (age-adjusted reference range)	Latest IGF-I (age-adjusted reference range)	Peg dose (mg)	Plasma concentration of Peg (ng/ml)	Duration of treatment with Peg (years)	Serum GH prior to Peg (mU/l)	Serum GH after 6 months Peg (mU/l)	Serum GH after 12 months Peg (mU/l)	Serum GH after 24 months Peg (mU/l)
1	1200 (126–369)	369 (126–369)	40	47 196	2	218	232*	346	250
2	987 (126–369)	157 (126–369)	20	24 412	2	34	13.4*	15.2	11.2
3	1463 (114–492)	397 (114–492)	40	28 308	1	54	152	N/A	N/A
4	587 (126–369)	258 (126–369)	15	40 416	2	14.4	24*	38	26
5	1026 (126–369)	228 (126–369)	30	26 777	1	36	52	86	N/A
6	494 (108–263)	215 (108–263)	15	7 571	1	5.6	11.2	15.8	N/A
7	682 (108–229)	185 (108–229)	20	18 683	2	34	32*	50	36

N/A = not assessed.

*Treatment with pegvisomant was weekly for the first 6 months.

eight substituted residues in the region of site one binding and one substitution in the region of site two, dictates that it binds to the GH receptor more avidly than wild-type GH, but receptor signalling and subsequent IGF-I generation are prevented. The addition of 4–5 polyethylene glycol moieties reduces the antigenicity (and also the receptor avidity) of the foreign peptide and prolongs its half-life in plasma from under 10 min to in excess of 72 h (26). Pegvisomant does not attempt to lower circulating GH concentrations; in fact, serum GH levels increase (16), such that GH cannot be used as a measure of disease activity. Further, high homology between pegvisomant and wild-type GH means that the drug is detected by most routine GH assays, producing spuriously elevated serum GH levels (27). Serum IGF-I is the obvious primary measure of disease activity in patients receiving pegvisomant. In a 12-week, double-blind placebo-controlled study of a heterogeneous group of 112 patients with active acromegaly (16), pegvisomant was shown to be a highly effective therapy, judged by symptomatic improvement and lowering of serum IGF-I levels into the age-related reference range in 89% of patients receiving 20 mg daily.

In contrast to all other modalities of treatment (surgery, radiotherapy, dopamine agonists and SST analogues), in which the pretreatment GH level is a major determinant of the likelihood of therapeutic success, pegvisomant appears able to normalise serum IGF-I levels in even the most severe cases of acromegaly, such as those reported here (Fig. 1 and Table 2), irrespective of the pre-pegvisomant serum GH/IGF-I values. As Table 2 suggests, patients with higher starting serum IGF-I levels require higher doses of pegvisomant, but there is no evidence that 40 mg daily, the largest dose used here, is at the top of the dose–response curve for pegvisomant. Rather, it appears that the serum concentration of drug is crucial and that patients with higher serum GH/IGF-I values require larger doses of drug in order to achieve greater plasma levels of drug effectively to antagonise endogenous ligand (Table 2) but that this can be given safely. Such high serum concentrations of drug are necessary as pegylation of the GH receptor antagonist significantly reduces its affinity for the GH receptor.

This report details the use of pegvisomant to achieve biochemical control of acromegaly in a group of patients whose disease was resistant to established medical therapies. As in one earlier report (28), serum IGF-I was normalised in all the previously treatment-resistant patients studied here (Fig. 1) and, commensurate with this, there was improvement in the symptoms and signs of acromegaly. This response was maintained over the duration of the study (2 years in four of the patients and 1 year in the remaining three), with no dose increments required once maintenance dose had been achieved, judged by a serum IGF-I level within the age-related reference range. Hence, it

appears that efficacy is maintained, although longer term follow-up is clearly required.

All patients have had at least 6-monthly MRI scans of the hypothalamo–pituitary region throughout the study, because of the theoretical possibility that interruption of the GH/IGF-I feedback loop may promote pituitary tumour growth. There was no evidence of tumour expansion in any of the seven patients, including a patient (no. 1) with a very aggressive locally invasive tumour with infratemporal and infraorbital extensions. Continued radiological surveillance is clearly mandatory. In the recently published clinical trial (29), serum GH concentrations rose significantly, over 2 weeks, in pegvisomant-treated patients compared with placebo-treated patients but there was no statistically significant change between 2 weeks and the conclusion of the study (12 weeks). Our data are complicated by the fact that all patients had previously received pituitary irradiation, but a progressive rise in serum GH concentrations does not appear to have occurred during pegvisomant therapy in this study (Table 2).

In summary, we have highlighted the ability of pegvisomant, a novel GH receptor antagonist, to improve symptoms and signs and normalise serum IGF-I levels in patients with acromegaly refractory to conventional medical therapy. Treatment was well tolerated and efficacy was maintained over 2 years of therapy. The role of pegvisomant in the medical management of acromegaly remains to be determined.

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