Pegvisomant: an advance in clinical efficacy in acromegaly

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Abstract

Acromegaly is a chronic disorder invariably caused by a growth hormone (GH)-secreting pituitary tumour and is characterised by disabling symptoms (sweating, arthralgia, headache, paraesthesiae, fatigue), significant comorbidities (diabetes mellitus, hypertension, sleep apnoea), and premature mortality. Symptomatic control can be achieved by lowering insulin-like growth factor-I (IGF-I) concentrations to within the age-adjusted normal range, and survival can be improved to match that of the general population. However, even with optimal surgery and current medical therapies (dopamine agonists, somatostatin analogues), 30% to 50% of patients do not achieve target concentrations of IGF-I and GH.

Pegvisomant is a new GH-receptor antagonist that blocks GH activity by inhibiting functional dimerisation of GH-receptors. Given as subcutaneous injections at dosages of 10 mg, 15 mg, or 20 mg/day for 3 months, pegvisomant normalised serum IGF-I concentrations in, respectively, 54%, 81%, and 89% of acromegalic patients. Moreover, long-term pegvisomant therapy normalised IGF-I concentrations in 97% of patients treated for 12 months or longer, with no evidence of tachyphylaxis. Pegvisomant is the most effective medical therapy, reported to date, in terms of normalisation of circulating IGF-I concentrations. In addition, pegvisomant appears to be safe and well tolerated. Although additional long-term studies are required to further assess safety, the introduction of this innovative treatment should allow for optimal disease control in patients with acromegaly.

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Introduction

Acromegaly is a debilitating disorder that results from long-term exposure to elevated concentrations of growth hormone (GH). Caused by a GH-secreting pituitary tumour in most cases, acromegaly is characterised by disabling symptoms such as sweating, arthralgia, headache, paraesthesia, and fatigue (1). GH-induced bone and soft tissue proliferation can result in acral enlargement, cardiomyopathy, sleep apnoea, and snoring; moreover, acromegaly can cause diabetes and hypertension. All of these problems contribute to an increased risk of premature mortality in patients with uncontrolled acromegaly.

The mortality rate for uncontrolled acromegalic patients is two to three times that of the general population, but effective treatment can improve survival to match that of the age-matched population (2). Although currently available treatments have not been shown to completely normalise insulin-like growth factor-I (IGF-I) and GH concentrations, newer therapies in development – such as the GH-receptor antagonist pegvisomant – have shown great promise.

This article provides an overview of current treatment strategies for acromegaly, highlighting the need

for newer, more effective treatments. An in-depth review of data from clinical trials of pegvisomant, a new GH-receptor antagonist, is also provided.

Current management strategies for acromegaly

In patients with acromegaly, the primary clinical goals of treatment are to alleviate symptoms, reduce tumour mass, prevent tumour recurrence, and improve long-term outcomes. Symptomatic control can be achieved by reducing IGF-I concentrations to within the age-adjusted normal range and by lowering GH concentrations to normal (3). Several studies have demonstrated that mortality rates return to normal when GH concentrations are lowered to <5 mU/l (<2.5 µg/l), and one study has extended this to normalisation of IGF-I concentrations (4–7) (Table 1). Based on these findings, the therapeutic goal is to attain post-treatment GH concentrations of <2.5 µg/l with normalisation of IGF-I serum concentration to the age-adjusted normal range.

Surgery is the treatment of choice for acromegaly, unless contra-indicated. If surgery fails to reduce

Table 1 Mortality in acromegaly is related to IGF-I and GH concentrations.

Study	Patients (n)	Mortality (SMR)	Relationship to GH/IGF-I
Swearingen <i>et al.</i> (5)	162	1.16	• SMR 0.86 in patients with normal serum IGF-I concentrations • SMR 1.8 in those with increased serum IGF-I concentrations
Orme <i>et al.</i> (7)	1362	2.5	• SMR 1.2 in patients with post-treatment serum GH concentrations <2.5 µg/l • SMR 2.12 in those with serum GH concentrations >10 µg/l
Rajasoorya <i>et al.</i> (6)	151		• Mortality correlated with latest GH measurement ($P < 0.0001$)
Bates <i>et al.</i> (4)	79	2.7	• SMR 1.42 in 31 patients with serum GH concentrations <2.5 µg/l

SMR, standardised mortality ratio.

IGF-I and GH to the desired concentrations, adjuvant treatment with pituitary radiotherapy or other medical therapies is indicated.

Surgery

Transsphenoidal surgery is the most rapid means of reducing serum IGF-I and GH in patients with acromegaly. The proportion of patients achieving GH levels <2.5 µg/l, however, varies by treatment centre, ranging from 24% to 76%. There is evidence to suggest that the differences in surgical outcome may be attributed, in part, to the skill of the surgeon (8, 9). For example, results from centres where several surgeons operate on relatively few cases are often poor, with response rates as low as 24% (9). In contrast, treatment centres where a single dedicated surgeon performs the majority of transsphenoidal procedures report much better results, suggesting that successful outcomes depend on the skill of the surgeon (10–12). In one centre, surgical cure rates nearly doubled, increasing from 33% to 64% ($P < 0.0005$) when one compared with eight surgeons performed transsphenoid surgery (13).

Tumour size also affects the likelihood of surgical success. Based on surgical data from more than 1000 patients, surgery (conducted in centres of excellence) achieved target GH serum concentrations in 85% to 90% of patients with microadenomas (i.e. tumours <1 cm), but only 50% to 55% of patients with macroadenomas achieved the desired reduction in GH concentration (1). Unfortunately, far more patients with acromegaly present with macroadenomas (approximately 70%) than with microadenomas; thus, approximately 40% of patients will continue to have unacceptably high concentrations of IGF-I and GH after surgery, a finding that emphasises the critical need for effective adjuvant therapies.

Adjuvant medical therapy

Adjuvant treatments for acromegaly include radiotherapy, dopamine agonists, and somatostatin analogues. Although a complete discussion of pituitary radiotherapy is beyond the scope of this article, it should be noted that pituitary radiotherapy is effective as an

adjunct to surgery. However, radiotherapy takes many years to reduce IGF-I and GH concentrations to acceptable levels; thus the use of additional medical therapies to alleviate symptoms may be required in the interim.

Dopamine agonists Dopamine agonists (e.g. cabergoline and bromocriptine) bind to D₂ receptors in the pituitary and suppress GH secretion in some patients with acromegaly; the exact mechanism of this effect is unclear. Although these agents have been shown to reduce GH concentrations, they rarely do so to an acceptable level (14). Review of the literature indicates that less than 10% of patients will experience normalisation of IGF-I and less than 20% of patients will achieve GH concentrations of <5 µg/l (2). Higher doses of cabergoline may be more effective, but future studies are required (15).

Somatostatin analogues Octreotide is a long-acting synthetic somatostatin analogue that is administered subcutaneously three times daily and has demonstrated efficacy in the treatment of acromegaly. In two clinical studies, 22% to 40% of patients achieved GH concentrations <2.5 µg/l (16, 17), and in a third study, 45% of patients achieved GH concentrations <5 µg/l (18). IGF-I, which mediates the effects of GH, was normalised in less than half (45%) of these patients. The use of somatostatin analogues may be limited because of a reduction in gall-bladder motility that may be associated with the development of gallstones. These typically occur in approximately 5% to 20% of patients (19, 20).

Long-acting somatostatin analogues are a more effective and convenient means of IGF-I normalisation in patients with acromegaly, and include octreotide LAR and lanreotide. Because these long-acting intramuscular depot preparations allow patients to receive once-monthly injections, they are considerably more convenient than the original octreotide formulation. However, a substantial proportion (approximately 35% to 50%) of patients treated with long-acting somatostatin analogues will still fail to achieve normalisation of IGF-I and GH concentrations, again underscoring the need for more effective treatments (1).

Pegvisomant: a novel approach to the treatment of acromegaly

Pegvisomant represents an innovative concept in the medical management of acromegaly. Pegvisomant binds to GH receptors on the cell surface, where it blocks GH signal transduction and thereby inhibits GH activity, including IGF-I production (for a full description, please see the article in this supplement, pp S21–S25 (21) by John Kopchick). Because pegvisomant inhibits GH activity (and not GH secretion), serum GH concentrations are not a valid marker for treatment efficacy – serum IGF-I concentrations are the best marker of efficacy in patients treated with pegvisomant. Most importantly, the efficacy of this GH-receptor antagonist is relatively independent of tumour status. In other words, the effects of pegvisomant, unlike somatostatin analogues or dopamine agonists, are not dependent on the dopamine or somatostatin receptor density of the tumour.

Clinical efficacy of pegvisomant

The efficacy of pegvisomant has been evaluated in a double-blind, placebo-controlled study of 112 patients with active acromegaly and serum IGF-I concentrations $\geq 30\%$ above the upper range of the age-adjusted normal range. Baseline demographic and clinical characteristics are provided in Table 2 (21). Patients were randomly assigned to receive subcutaneous injections of 10 mg, 15 mg, or 20 mg pegvisomant or placebo once daily for 3 months. Efficacy measures included the proportion of patients achieving normalisation of serum IGF-I, changes in well-being, and improvement in soft tissue swelling.

Pegvisomant given at doses of 10, 15, or 20 mg/day normalised circulating IGF-I concentrations in 54%, 81%, and 89% of patients respectively (Fig. 1). In contrast, only 10% of patients receiving placebo achieved normal IGF-I concentrations (21). All three pegvisomant treatment groups demonstrated

statistically significant decreases in serum IGF-I concentrations compared with placebo, with the greatest mean decrease from baseline (60%) seen in the 20-mg pegvisomant group (Fig. 2).

Significant improvements were also seen in overall well-being in pegvisomant-treated patients compared with placebo (Fig. 3) and in individual symptom scores for perspiration, fatigue, and paraesthesiae. Improvements in soft tissue swelling were demonstrated by the mean reduction in ring size (as measured using European jewellers' rings), with significant improvements seen in patients receiving the 15-mg or 20-mg pegvisomant dose (Fig. 3).

Long-term efficacy results

Many patients from the initial 12-week study of pegvisomant went on to participate in a long-term extension

Figure 1 Percentage of patients achieving normal age-related serum IGF-I concentration at any visit after baseline treated daily with pegvisomant or placebo. * $P < 0.0001$ vs placebo. (Data source: (22).)

Figure 2 Mean percentage of baseline serum IGF-I concentrations in 111 acromegaly patients treated with daily pegvisomant or placebo injections for 3 months. * $P < 0.0001$ vs placebo.

Table 2 Baseline characteristics of 112 patients with acromegaly.

Characteristic	Patients, n (%)
Sex	
Men	63 (56)
Women	49 (44)
Mean age (years)	47.5 (range 20–78 years)
Mean weight (kg)	92 (range 50–158 kg)
Prior therapies	
Surgery	93 (83)
Conventional radiotherapy	57 (51)
Gamma knife radiotherapy	7 (6)
Somatostatin analogue	81 (72)
Dopamine agonist	55 (49)

(Reprinted, with permission, from (22).)

Figure 3 Improvement in (A) overall patient well-being (low score indicates greater well-being than high score) and (B) patient ring size, an objective measure of soft-tissue swelling. (Data source: (22).)

trial (22). This second study investigated the effects of daily pegvisomant injections when given during a period of up to 18 months, to determine the long-term efficacy and safety of pegvisomant. Development of antibodies against GH and pegvisomant was assessed since that could also affect long-term efficacy. Magnetic resonance imaging (MRI) was used to monitor changes in tumour volume. Pegvisomant dosing began at 10 mg/day, and was titrated as necessary in 5-mg increments until normalisation of IGF-I occurred or the maximum dose of 40 mg/day was reached.

One hundred and sixty patients were enrolled in the study; baseline demographic and clinical characteristics are shown in Table 3. Long-term efficacy data for patients who were treated for 6 months ($n = 131$), 12 months ($n = 90$), or 18 months ($n = 39$) are shown in Fig. 4. As might be expected with inhibition of GH signal transduction, serum GH concentrations increased during the first 2 weeks of therapy; however, no further increases were noted after that time, and there was no evidence of tachyphylaxis. Notably, normal serum IGF-I concentrations were achieved in 97% of patients treated with a mean dose of 18 mg/day for 12 months, a better response than that achieved with any other medical therapy to date (22).

Long-term pegvisomant therapy also improved the metabolic parameters of acromegaly. Significant

Table 3 Baseline demographic and clinical characteristics in 160 patients receiving long-term pegvisomant therapy.

Characteristic	Patients, n (%)
Sex	
Men	94 (59)
Women	66 (41)
Mean age (years)	46 (S.D. ± 14)
Mean weight (kg)	94 (S.D. ± 21)
Serum GH ($\mu\text{g/L}$)	10.2 (S.D. ± 16.0)
Serum IGF-I ($\mu\text{g/L}$)	762 (S.D. ± 330)
Mean pituitary tumour volume (cm^3)	2.39 (S.D. ± 3.45)
Prior therapies	
Surgery	134 (84)
Radiation	94 (59)
Somatostatin analogue	117 (73)
Dopamine agonist	76 (48)

S.D., standard deviation.

(Adapted and reprinted, with permission, from (23).)

decreases were observed in fasting insulin levels at 12 and 18 months with a corresponding decrease in serum glucose concentrations (Fig. 5). Thus, the blockade of GH signal transduction lowered insulin, lowered glucose, and improved insulin sensitivity.

Overall, 17% of patients developed anti-pegvisomant antibodies; however, titres were low and efficacy was not compromised. Mean pituitary tumour volumes did not change in patients with an average of 11.5 months of follow-up, regardless of the patients' history of radiation therapy (Fig. 6). Although two patients required treatment for tumour progression, both tumours were very invasive from the outset, and there was no clear evidence that pegvisomant played a role in the expansion of either tumour (22).

In summary, pegvisomant therapy resulted in normalised IGF-I concentrations in 97% of 90 patients treated with a mean dose of 18 mg/day for 12 months.

Figure 4 Serum IGF-I (solid lines) and GH (broken lines) concentrations after 6, 12 and 18 months of pegvisomant therapy. (Adapted and reprinted, with permission, from (23).)

Figure 5 Serum insulin (solid lines) and glucose (broken lines) concentrations after 6, 12 and 18 months of pegvisomant therapy. * $P < 0.05$, † $P < 0.01$ vs 0 months. (Data source: (23).)

Patients who received pegvisomant for up to 18 months showed no evidence of tachyphylaxis, and insulin sensitivity was improved. The efficacy of pegvisomant was not affected by the development of anti-pegvisomant antibodies, and with the possible exception of two cases, there was no evidence of pegvisomant-induced tumour progression.

Pegvisomant safety and tolerability

Pegvisomant therapy was generally well tolerated. The most common adverse events were consistent with those found in other long-term studies: infection (primarily non-serious upper respiratory infections rarely requiring treatment), headache, and pain (Table 4) (22). Injection-site reactions occurred in 18 of 160 patients receiving pegvisomant; they were categorised as mild, erythematous reactions that resolved without

Table 4 Adverse events occurring in $\geq 10\%$ of patients receiving long-term pegvisomant therapy ($n = 160$).

Adverse event	Patients, n (%)
Infection	52 (33)
Headache	41 (26)
Pain	36 (23)
Influenza-like syndrome	33 (21)
Accidental injury	28 (18)
Diarrhoea	23 (14)
Hypercholesterolaemia	23 (14)
Back pain	21 (13)
Asthenia	21 (13)
Arthralgia	19 (12)
Injection-site reaction	18 (11)
Sinusitis	16 (10)

(Adapted and reprinted, with permission, from (23).)

treatment. Of the 160 patients treated with pegvisomant, two patients had deranged liver function tests (increased serum alanine aminotransferase and aspartate transaminase) and discontinued treatment. Neither patient exhibited symptoms, but in one case rechallenge with pegvisomant was once again associated with hepatitic liver function tests. Two patients experienced an increase in pituitary tumour size (described previously) (22), but the cause of the increase was unclear. It seems more likely that this was related to the underlying aggressive nature of the tumour rather than to pegvisomant therapy itself.

Conclusions

Pegvisomant is currently the most effective medical therapy for normalising the circulating IGF-I concentrations in acromegaly. The drug appears to be safe and well tolerated. Because pegvisomant works by blocking the actions of GH, efficacy is independent of tumour characteristics, such as the density of somatostatin receptors. Additional long-term studies are required to monitor patients, but the introduction of this novel therapy into clinical practice improves the likelihood that optimal control is now attainable for nearly all patients with acromegaly.

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Figure 6 Lack of association between long-term pegvisomant therapy and changes in tumour size, as demonstrated by MRI scan results obtained while on pegvisomant. ●, patients received prior radiotherapy; ▲, patients untreated with radiotherapy. (Reprinted, with permission, from (23).)

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