

REGIONAL DRUG AND THERAPEUTICS CENTRE

**THE USE OF PEGVISOMANT IN THE
MANAGEMENT OF ACROMEGALY**

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January 2006



CONTENTS

SUMMARY	3
BACKGROUND	5
EFFICACY	6
Tumour growth	9
Cardiovascular risk.....	9
Bone turnover markers.....	10
ADVERSE EFFECTS	11
DOSAGE, ADMINISTRATION AND COST	11
PLACE IN TREATMENT	14
ARRANGEMENTS FOR PRESCRIBING	15
FUTURE DEVELOPMENTS.....	15
ACKNOWLEDGEMENTS	15
REFERENCES	16
APPENDICES.....	18
Appendix I: Summary of trials	18

SUMMARY

- **Acromegaly is a rare chronic debilitating disease with an estimated incidence of 4-6 cases per million per year and a prevalence of 4-6 cases per 100,000 people. It is due to excessive secretion of growth hormone (GH) and a resulting increase in the production of insulin-like growth factor I (IGF-I), usually caused by a benign GH-secreting pituitary adenoma. Patients with untreated acromegaly have approximately twice the mortality rate of healthy individuals matched for age. Currently available treatments consist of radiation therapy, surgical removal of the adenoma and drug treatment with dopamine agonists and/or somatostatin (SMS) analogues. Surgery remains first-line therapy with a cure rate of around 60%. A third of patients do not respond to surgery, radiation therapy or conventional drug treatment.**
- **Pegvisomant is licensed for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with SMS analogues did not normalise insulin-like growth factor I (IGF-I) concentrations or was not tolerated.**
- **In a 12-week randomised controlled trial (RCT) of pegvisomant, the number of patients achieving normalisation of serum IGF-I concentrations increased dose-dependently with 82% of patients treated with pegvisomant 20 mg/day achieving IGF-I normalisation. Increasing doses of pegvisomant statistically significantly reduced the primary efficacy endpoint of percentage change in serum IGF-I concentration from baseline compared with placebo. Scores for individual symptoms and signs also decreased in all the pegvisomant groups. In a further trial, which extended up to 18 months, normal serum IGF-I concentrations were achieved in 97% of patients treated for 12 months or more.**
- **The most commonly reported adverse events were asthenia, headache, sweating and injection site reactions. Serum aspartate transaminase (AST) and alanine aminotransferase (ALT) levels should be monitored at 4- to 6-week intervals for the first 6 months.**
- **Pegvisomant treatment resulted in significant decreases in markers of bone formation and bone resorption with normalisation of IGF-I levels. However, the net impact of decreased bone turnover on bone mineral density cannot yet be determined. To date, there is no evidence that pegvisomant induces tumour growth, but it should be noted that it would not protect against this risk in non-irradiated patients with aggressive tumours.**
- **Pegvisomant is a third-line option for those patients in whom surgery and/or radiotherapy and conventional medical therapy have been unable to effect a cure/remission or in those unable to tolerate or who are unresponsive to dopamine agonists or SMS analogues.**

- **Pegvisomant should only be initiated by tertiary care specialists experienced in the full range of treatment modalities available for acromegaly. It will be indicated in a small minority of patients. Consideration should be given to limiting its use to one or a few centres to maximise experience with the drug.**
- **Assuming that one-third of the 4-6 patients with acromegaly per 100,000 population in the UK are intolerant of or do not respond to other treatments, 1-2 patients per 100,000 population may be eligible for treatment with pegvisomant. At a dose of 20 mg/day, this equates to an annual cost of £36,500 to £73,000 per 100,000 population. However, if pegvisomant is reserved for only the most extreme cases, usage and costs may be less than this.**
- **Trials investigating the effects of long-term pegvisomant treatment are required, specifically with regard to establishing whether continually raised GH concentrations that occur with this treatment affect tumour growth.**

BACKGROUND

Acromegaly is a rare chronic debilitating disease resulting from excessive secretion of growth hormone (GH) and a resulting increase in the production of insulin-like growth factor 1 (IGF-I).^{1, 2} It is usually caused by a benign GH-secreting pituitary adenoma (somatotroph adenoma).² The symptoms of acromegaly can involve any organ or system causing tissues to increase in size.³ Patients with untreated acromegaly have approximately twice the mortality rate of healthy individuals matched for age. Mortality is generally attributable to cardiovascular, cerebrovascular and respiratory disorders and cancer.^{2, 3, 4} All patients should therefore be treated, even if asymptomatic. Furthermore, acromegaly can lead to disfigurement and substantial complications from the sellar mass, such as visual field defects, blindness and headaches.² Acromegaly is not very common with an estimated incidence of 4-6 cases per million per year and a prevalence of 4-6 cases per 100,000 population.³ The goal of treatment is to reverse the effects of the hypersecretion of GH and normalise the production of IGF-I. Effective treatment ameliorates the symptoms and signs of the disease and lowers the mortality rate.¹

Currently available treatments consist of radiation therapy, surgical removal of the adenoma and drug treatment, often in combination. Surgery cures around 60% of patients, and less than half of those with large tumours (the majority of patients).^{1, 2, 4} External beam radiation therapy (EBRT) may be used in those not cured, unfit for or unwilling to undergo surgery.⁵ Most studies have used the serum GH concentration as a 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-EBRT levels by 5 years.⁵ Radiotherapy is often characterised by delayed and variable effect, poor efficacy and a high incidence of panhypopituitarism.^{1, 2} Medical therapy is usually directed toward those who have active disease despite surgery (pending the longer term effects of radiotherapy), those unsuitable for surgery and those with specific symptoms requiring treatment prior to surgery and/or radiotherapy. Available drug treatments are dopamine agonists, such as bromocriptine, pergolide and cabergoline, somatostatin (SMS) analogues, such as octreotide and lanreotide, and the new GH receptor antagonist pegvisomant.²

In the anterior pituitary, dopamine binds to the predominating D₂ receptors with the overall effect of suppressing the synthesis and secretion of prolactin, thyrotropin and GH. As dopamine receptors are present on human somatotrophs, the effects of dopamine antagonists are probably exerted directly. In healthy individuals, acute administration of dopamine agonists cause GH release, but in the majority of patients with acromegaly, treatment with dopamine agonists paradoxically inhibits GH secretion.^{2, 4} The reason for this discrepancy is unclear.² Overall, dopamine agonists have limited efficacy and tolerability and, therefore, compliance may be poor.^{1, 2} However, due to their oral route of administration and low cost a trial of dopamine agonists therapy is often employed before SMS analogues are considered. Dopamine agonists may also be used in conjunction with SMS analogues.⁴

Long-acting SMS analogues, such as octreotide or lanreotide, given every 2-4 weeks, inhibit the secretion of GH, normalising the production of IGF-I in about 50%-65% of patients.^{1, 2} SMS analogues also alter the regulation of secretion of many hormones, including insulin, glucagon and thyroid-stimulating hormone.⁴ Short-term suppression of GH by SMS analogues in patients with acromegaly has been shown

to depend on the number of somatostatin receptors on the somatotroph adenoma.² Overall, treatment with SMS analogues results in tumour shrinkage in up to 30% of patients.²

The understanding of the mechanism by which GH interacts with its receptor has facilitated the development of GH receptor antagonists, of which pegvisomant, an analogue of human GH, is the first to be available.² The efficacy of pegvisomant is independent of any characteristics of the somatotroph tumour; pegvisomant blocks the ability of GH to stimulate production of IGF-I, the main mediator of the somatotrophic actions of GH.¹ In patients with acromegaly treated with pegvisomant, IGF-I falls but circulating GH does not and, therefore, the serum GH concentration cannot be used as a therapeutic marker.³ Pegvisomant has been pegylated to increase its half-life and to reduce the likelihood of antibody formation.²

In acromegaly, cure can generally be defined as normalisation of serum GH and IGF-I concentrations.² GH pulsatility should also be normal and be suppressed after an oral glucose load. Strict biochemical criteria have been defined and, according to these, cure is defined as circulating IGF-I levels that are reduced to an age-adjusted normal range and a nadir GH after an oral glucose load of <1 microgram/l. Normalisation of IGF-I is associated with reduction in the excess mortality associated with acromegaly and is therefore an essential criterion of the definition of cure. However, GH levels <2.5 microgram/l are associated with a reduction in mortality in acromegaly patients, but unfortunately, are not always associated with normal IGF-I levels.²

The purpose of this report is to evaluate the efficacy and safety of the GH antagonist pegvisomant for the treatment of acromegaly. There is no firm consensus or systematic review on whether surgery or medical treatment is best for the primary treatment of acromegaly and the place of radiotherapy in the management of acromegaly is also subject to debate.³

EFFICACY

Pegvisomant (Somavert[®], Pfizer Limited) is a genetically engineered analogue of human GH that antagonises the action of GH,^{1,6} thereby suppressing production of IGF-I, the main mediator of the somatotrophic actions of GH¹ in patients with acromegaly.² Currently, pegvisomant is the only available member of this new class of GH-receptor antagonist drugs. It is licensed in the UK for the treatment of acromegaly in patients who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalise IGF-I concentrations or was not tolerated.⁶ Normalisation of serum IGF-I concentrations within the age-adjusted normal range and the maintenance of an optimal therapeutic response are the main aims of treatment as these reduce the associated increased morbidity and mortality.

A double-blind, multinational, phase III, 12-week randomised controlled trial (RCT) of three different daily doses of subcutaneous (SC) pegvisomant (10 mg, 15 mg or 20 mg) and placebo was carried out in 112 (63 male; 49 female) acromegalic patients.¹ The diagnosis of acromegaly was established on the basis of symptoms and signs at presentation and evidence of a pituitary adenoma. The inclusion criteria required the serum IGF-I concentrations to be at least 1.3 times the upper limit of the age-

adjusted normal range. Previous medical therapy was withdrawn at least two weeks after the initial screening visit and the second screening visit took place a minimum of two and five weeks after the discontinuation of SMS analogue and dopamine-agonist therapy, respectively. Patients who had received a long-acting SMS analogue within 12 weeks before enrolment were not eligible for the study. Of those enrolled, 93 had undergone pituitary surgery, 57 of whom had also had radiotherapy, six had undergone radiotherapy without surgery, nine had received only drug therapy and four had received no prior therapy. Eighty-one patients had previously been treated with SMS analogues and 55 with dopamine agonists.

In order to decrease the time required to reach steady state, all participants were given a loading dose of either 80 mg pegvisomant or placebo. The onset of action of pegvisomant was rapid, but the contribution of the loading dose to this is unknown.¹

At 12 weeks, the primary efficacy endpoint of percentage change in serum IGF-I concentration from baseline was statistically significantly reduced by increasing doses of pegvisomant: -26.7%, -50.1% and -62.5% in the 10-mg, 15-mg and 20-mg groups, respectively, compared with placebo (-4.0%; $p < 0.001$ for each group vs. placebo).¹ Between-dose differences for the percentage change in the serum IGF-I concentration from baseline for pegvisomant were also statistically significant ($p = 0.005$ and $p < 0.001$ for 15 mg and 20 mg, respectively, vs. 10 mg, and $p = 0.02$ for 20 mg vs. 15 mg). The number of patients whose serum IGF-I concentrations were normal at 12 weeks increased dose-dependently: 38%, 75% and 82% in the 10-mg, 15-mg and 20-mg groups, respectively, compared with 10% of the placebo group ($p < 0.001$ vs. placebo for the 20-mg and 15-mg groups; $p = 0.02$ vs. placebo for 10 mg). Unfortunately, the efficacy analysis was not an intent-to-treat analysis, no sample size or power calculations are shown and confidence intervals are not provided.

A questionnaire designed to evaluate five symptoms and signs of acromegaly (soft-tissue swelling, arthralgia, headache, excessive perspiration and fatigue) showed that the mean scores for the individual symptoms and signs increased slightly in the placebo group and decreased in all the pegvisomant groups. Significant decreases were seen individually for soft-tissue swelling (20 mg/day), excessive perspiration and fatigue (both 15 and 20 mg/day).¹ A further measurement of ring size of the fourth digit of the right hand was conducted. Ring size decreased in a dose-dependent fashion in all pegvisomant groups and was significantly lower in the 15-mg and 20-mg groups compared with placebo ($p = 0.001$ and $p < 0.001$, respectively).¹

Serum GH concentrations increased and then plateaued in the pegvisomant groups in a dose-dependent fashion that coincided with the magnitude and timing of the reduction in serum IGF-I concentrations. Serum anti-GH antibodies were found in titres ranging from 1:4 to 1:64 in five patients treated with 10 mg pegvisomant, one treated with 15 mg and two treated with 20 mg. No patient had a significant change in tumour volume during the study,¹ but as the adenomas are slow growing this would be expected in a short trial.

Overall, four patients withdrew from the study, two from the placebo group (one each due to persistent headache and tumour compression of the optic chiasm) and two from the pegvisomant 15-mg group (one each due to persistent headache and raised hepatic aminotransferases).

In this trial, the population was mixed and no separate analysis based on previous treatment exposure was carried out. Further trials to determine whether the magnitude of the response to pegvisomant is affected by previous therapy would be useful.

In a multinational, open-label, uncontrolled, observational, dose-titration study financed and designed by the manufacturer, 160 patients were started on pegvisomant 10 mg daily and titrated up or down, as necessary, by 5 mg/day, until the serum IGF-I concentration was normal or a maximum of 40mg/day was reached.⁷ Patients were recruited from the placebo-controlled trials SEN-3614/15 (described above) and SEN-3613A, in which 38 patients were initially treated with weekly doses of pegvisomant before being switched to daily dosing. Only the daily dosing data are included in the efficacy analysis. In protocol SEN-3614/15, dose adjustments could not be less than eight weeks apart. The patient selection eligibility criteria were the same as those for entry into the controlled trial SEN-3614/15 described above.⁷

No specific exclusion criteria are stated, but of the 167 patients who participated, seven received only placebo and were excluded from all analyses, three received only a single dose of pegvisomant and five received only weekly doses. Data from the latter eight patients were excluded from the efficacy analyses (n=152) but were included in the safety analyses (n=160). Of the 160 patients (94 male; 66 female) exposed to pegvisomant, 30 withdrew prematurely – two for protocol violations, nine for adverse events, five for lack of efficacy, two were lost to follow up and 12 withdrew voluntarily.

The primary efficacy endpoint is not explicitly stated; however, the authors state that treatment efficacy was assessed by measuring changes in tumour volume determined by magnetic resonance imaging (MRI) and serum GH and IGF-I concentrations. In order to assess the effects of pegvisomant on IGF-I and GH, patients were placed in cumulative cohorts depending on whether they had completed 6, 12 or 18 months of continuous daily pegvisomant therapy. Mean serum IGF-I and GH concentrations at baseline were higher for the 18-month cohort (n=39) than for the group as a whole and this was attributed to the more severe disease of patients entered into the earliest phase of clinical development. A graph shows that dose-titrated decreases in serum IGF-I concentrations, as required by the protocols, were achieved in all three cohorts; however, neither actual figures nor percentage changes from baseline are presented. Normal serum IGF-I concentrations were achieved in 87 (97%) of 90 patients treated for 12 months or more. In 11 patients treated for more than a year, IGF-I decreased to below age-adjusted normal limits and nine of these required a decrease in dose.⁷

Durability of the response was assessed in 38 patients treated for an average of 83 weeks; the IGF-I levels of these patients were within normal limits in 91.7% of the post-baseline visits. Mean serum GH concentrations remained relatively stable with increases of 12.5, 12.5 and 14.2 microgram/l for the 6-, 12- and 18-month cohorts, respectively (p<0.05 for within-cohort baseline vs. final comparison).⁷

In 78 patients previously treated with radiation therapy, the mean tumour volume decreased by -0.126 cm^3 over 12.5 months (p=0.214), and in 53 patients previously untreated with radiation therapy, the mean tumour volume increased by 0.103 cm^3 over 10.0 months (p=0.948). No association between duration of pegvisomant treatment and change in tumour volume was demonstrated.

Overall, the uncontrolled nature of the study makes it impossible to draw conclusions about the potential for certain adverse events, such as infections, to develop and the small number of patients in whom the durability of response was assessed indicate that these results may not necessarily reflect the longer-term use of pegvisomant.⁷ Two patients had raised liver aminotransferases necessitating withdrawal of the drug, suggesting that caution is needed and liver function should be monitored until greater experience in use is obtained.⁷

Antibodies to pegvisomant were detected in 27 (16.9%) patients, but no tachyphylaxis was seen. The clinical significance of these antibodies is unknown.⁷

Significant decreases in insulin concentrations were seen in the 12-month ($p=0.0075$) and 18-month ($p=0.0393$) cohorts. Fasting serum glucose levels also decreased significantly in the 6-month ($p=0.0130$) and 18-month ($p=0.0125$) groups, but the decrease was non-significant in the 12-month group ($p=0.0531$). Glycated haemoglobin concentrations did not change significantly in any of the three cohorts.⁷

Tumour growth

An editorial accompanying the report of the trial discussed above⁷ suggests that pegvisomant is unlikely to be a primary treatment as it blocks hormone action rather than acting directly on the tumour itself.⁸ It is pointed out that the study does not answer whether the raised GH levels seen with pegvisomant treatment affect tumour growth, as pituitary tumours associated with acromegaly are slow growing. A divergent trend was observed in the above study, with tumour volumes decreasing slightly in patients who had received radiotherapy and increasing slightly in those who had not. There is no evidence that pegvisomant induced tumour growth, but it is noted in the editorial that pegvisomant would not protect against this risk in non-irradiated patients with aggressive tumours.⁸

The editorial also emphasises that epidemiological evidence has shown that the serum GH concentration is the single most important determinant of mortality in acromegaly. In 2000, a consensus workshop strongly recommended tight GH concentration control, which is not possible with pegvisomant.

A paper following on from that by van der Lely et al⁷ detailed the results of seven patients with persistent acromegaly, in whom adequate symptomatic and biochemical control could not be achieved following surgery and/or radiotherapy and medical therapy with octreotide and/or dopamine antagonists. These patients had participated in two previous clinical trials; three had completed one year of daily pegvisomant therapy and four had completed two years of therapy, six months of which was with weekly dosing.⁵ All patients had active acromegaly with serum IGF-I levels 30% above the upper limit of the age-related reference range. With a median dose of pegvisomant (20 mg/day) serum IGF-I levels decreased from a mean of 920 ng/ml to 258 ng/ml, which reflected normalisation of IGF-I levels within the age-related reference range for all seven patients.⁵ All patients had at least 6-monthly MRI scans, which showed no evidence of tumour expansion in any.

Cardiovascular risk

In the first part of a small three-part study, a cross-sectional study, conducted after withdrawal and washout from dopamine agonists or SMS analogues, 48 patients with acromegaly were compared with 47 age- and body mass index-matched healthy

controls. Those with acromegaly had lower C-reactive protein (CRP) levels (0.3 vs. 2.0 mg/l; $p < 0.0001$) and higher insulin levels (78.6 vs. 54.5 pM; $p = 0.0051$) than the controls. The serum lipoprotein(a), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), homocysteine and interleukin-6 levels of the groups did not differ significantly.⁹

In the second part, a 12-week placebo-controlled study, the 48 patients with acromegaly were randomised to either placebo ($n = 14$), pegvisomant 10 mg ($n = 12$), 15 mg ($n = 10$) or 20 mg ($n = 12$) daily.⁹ After 12 weeks, a *post hoc* analysis showed that the CRP level increased in all pegvisomant groups to varying degrees compared with placebo. The most significant change was seen in the pegvisomant 20-mg group, in which the CRP level increased by 13.7 mg/l compared with 0.5 mg/l in the placebo group ($p = 0.01$). No significant differences among the glucose, insulin, TG, total cholesterol, HDL-C, LDL-C, homocysteine or interleukin-6 levels of the groups were seen.

In the third and final part, all 48 patients entered an 18-month, open-label, longitudinal study, initially receiving pegvisomant 10 mg/day, adjusted by 5-mg increments at 8-week intervals to a maximum of 35 mg/day or until IGF-I levels were normalised to the age-related reference range. Thirty-four (71%) patients achieved normal IGF-I levels and entered the *post hoc* analysis. After IGF-I normalisation with pegvisomant, the CRP level increased by 2.0 mg/l ($p = 0.0002$), the total cholesterol and TG levels increased significantly whereas the lipoprotein(a) level decreased significantly and the glucose, insulin, homocysteine, HDL-C and interleukin-6 levels did not change.⁹

In summary, the paper concludes that patients with active acromegaly have low levels of CRP and that these levels increase in association with IGF-I normalisation during pegvisomant administration. The authors propose that the GH/IGF-I axis may be an important determinant of CRP levels. However, the significance of elevated CRP levels with pegvisomant treatment is unknown and the mechanism responsible and significance of this finding need to be clarified in further studies. This study was not powered to detect changes in the parameters studied above and all findings are therefore preliminary.⁹

Bone turnover markers

In a small trial of 27 patients randomised to receive either placebo, 10 mg, 15 mg or 20 mg pegvisomant daily, levels of two serum markers of bone formation, osteocalcin and carboxyterminal propeptide of type I procollagen (PICP), and a serum marker of bone resorption, cross-linked N-telopeptides of type I collagen (NTx), were determined at baseline and 12 weeks. Pegvisomant treatment resulted in significant decreases in all markers of bone formation and bone resorption with reduction of IGF-I levels.¹⁰ The authors state that it is not possible to discern whether the observed effects were due to GH receptor blockade or a reduction in IGF-I levels. Longer term studies are needed to determine whether the decrease in bone turnover persists and to determine the net impact of decreased bone turnover on bone mineral density, as this cannot be determined from serum markers. The independent effects of GH and IGF-I on bone metabolism also require elucidation.¹⁰

ADVERSE EFFECTS

Pegvisomant is generally well tolerated.^{1, 2} In clinical studies (n=160), the most commonly reported adverse events considered related to pegvisomant were injection site reactions (11%), sweating (7%), headache (6%) and asthenia (6%).^{6, 7} The only serious adverse effect seen was raised aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in one patient, who withdrew from the study, after eight weeks of treatment with pegvisomant 15 mg/day. These levels returned to normal within eight weeks of discontinuation of the study drug and rose again after a 4-week re-challenge with pegvisomant 10 mg/day.¹ Two patients (1.2%), one of whom is described above by Trainer et al¹, had increases in ALT and AST greater than 10 times the upper limit of normal within 12 weeks of beginning pegvisomant; the levels returned to normal within several months after drug discontinuation.⁷ Serum concentrations of the liver enzymes ALT and AST should be monitored every 4-6 weeks for the first six months of treatment with pegvisomant, or at any time in any patients exhibiting symptoms suggestive of hepatitis.⁶

An increase in serum GH levels mirroring the decrease in IGF-I concentrations occurs with pegvisomant treatment. Concerns have been raised about the relevance of this finding and the potential for tumour growth, although this has not been shown in trials to date.¹¹ Two cases of pituitary tumour expansion, which required treatment (radiotherapy in one patient and surgery in the other), in patients treated with pegvisomant have been reported.⁷ The cause of this is unclear.⁷ Patients should be carefully monitored in order to avoid any eventual progression in tumour size under pegvisomant treatment.⁶

Insulin sensitivity may increase following initiation of pegvisomant and there is a subsequent risk of hypoglycaemia in diabetic patients treated with insulin or oral hypoglycaemic agents, the doses of which sometimes need to be decreased.⁶

Serum antibodies against pegvisomant were detected in 16.9% of patients treated with pegvisomant. The clinical significance of these antibodies is unknown.⁶

DOSAGE, ADMINISTRATION AND COST

Pegvisomant comes in vials containing 10 mg, 15 mg and 20 mg dry powder with solvent for reconstitution. A loading dose of 80 mg pegvisomant should be administered by SC injection under medical supervision. Following this, pegvisomant 10 mg should be administered once daily as a SC injection.⁶ Vials should not be shaken vigorously during reconstitution as this might cause denaturation of pegvisomant. They are intended for single use and should be used immediately after reconstitution. Unreconstituted vials should be stored at 2-8°C and protected from light.⁶

Serum IGF-I concentrations should be measured every 4-6 weeks and appropriate dose adjustments made on the basis of these results in increments of 5 mg/day in order to maintain the serum IGF-I concentration within the age-adjusted normal range and to maintain an optimal therapeutic response. The maximum dose should not exceed 30 mg/day.⁶ GH levels are not used to measure the efficacy of pegvisomant as commercially available assays cannot distinguish between the drug and GH.⁶

No dose adjustments are necessary for elderly patients, but the safety and effectiveness of pegvisomant in patients with impaired renal or hepatic function has not been established. Pegvisomant should not be used during pregnancy or breastfeeding.⁶

Excluding VAT, the current cost of the pegvisomant 80-mg loading dose is £400 and the current annual cost of treatment (excluding the loading dose) is £18,250 for 10 mg/day, £27,375 for 15 mg/day and £36,500 for 20 mg/day. Should the maximum dose of 30 mg/day be required, the current annual cost rises to £54,750.¹²

Although pegvisomant is not licensed for once weekly administration, a prospective, open-label dose-finding study, published as a research letter, treated 26 acromegalic patients with both a long acting SMS analogue (octreotide 30 mg or lanreotide 120 mg) once monthly and pegvisomant once weekly.¹³ A median weekly dose of 60 mg pegvisomant was needed to return the IGF-I concentration to normal. The total annual cost (excluding VAT) per patient of treatment with pegvisomant 60 mg/week plus lanreotide or octreotide in the doses used in this study would then be £26,424-£28,350.^{12, 14, 15}

Assuming that one-third of the 4-6 patients per 100,000 population in the UK are intolerant of or do not respond to other treatments, 1-2 patients per 100,000 population may be eligible for treatment with pegvisomant. In one study⁷ the mean dose was 19.6 mg per day at 18 months. Therefore, a dose of 20 mg/day equates to an annual cost (excluding VAT) of £36,500 to £73,000 per 100,000 population. However, the usage of pegvisomant (and consequently the cost) could be substantially less than this, as it will only be used in the most extreme cases and in those who have previously undergone EBRT.¹⁶

The annual costs of pegvisomant¹² for 1-2 patients per 100,000 population and the SMS analogues octreotide¹⁴ and lanreotide¹⁵ are set out in the table below.

	Dose and frequency	Annual cost (excl VAT) per 100,000 population
Pegvisomant (for 1-2/100,000 population)	Loading dose of 80 mg, followed by 10 mg/day increased in increments of 5 mg/day to a maximum of 30 mg/day ⁶	£18,250 to £109,500 (80-mg loading dose costs £400)
Octreotide* (for 4-6/100,000 population)	100-200 micrograms by SC injection 3 times daily. ¹⁷ Once controlled may change to depot intramuscular (IM) injection - 20 mg every 4 weeks for 3 months to a maximum of 30 mg every 4 weeks. ¹⁸	SC injection £28,619 to £85,857 Depot injection £44,200 to £82,875
Lanreotide* (for 4-6/100,000 population)	30 mg by IM injection every 14 days then if necessary increase to 30 mg every 7 days, according to the patient's response. ¹⁹ A monthly depot injection is also available: 60 mg by deep SC injection every 28 days, adjust according to response (maximum of 120 mg assumed in this table). ²⁰	Standard injection £32,328 to £96,985 Depot injection £27,300 to £70,356

* octreotide and lanreotide are licensed for first line use

In practice, these costs may be slightly reduced as a result of dose adjustments.

Pegvisomant may be self-administered if the patient has sufficient dexterity and understanding to safely reconstitute and inject it. For some patients, administration by a district nurse may be required, which will increase the overall cost of treatment. Regular checking of serum IGF-I levels every 4-6 weeks and subsequent dose adjustments will increase costs further. There is no specific point at which serum IGF-I levels do not require monitoring. However, although there are no specific recommendations, the manufacturer (Pfizer) suggests that if the 4- to 6-weekly measurements show serum IGF-I levels consistently within the age-adjusted normal range, then, depending on clinical judgement, they could be measured at suitable periodic intervals with dose changes (up or down) as necessary.²¹

Serum AST and ALT levels should be monitored at 4- to 6-week intervals for the first six months of treatment or at any time in patients who exhibit symptoms suggestive of hepatitis.⁶

Treatment with pegvisomant does not reduce tumour size. All patients should be carefully monitored, usually by MRI, in order to avoid any eventual progression in tumour size. There is no indication of the frequency with which this would be required.⁶

PLACE IN TREATMENT

Pegvisomant is the first medical treatment for acromegaly that blocks GH binding, significantly and continuously, reducing IGF-I concentrations to the age-adjusted normal range in a significant number of patients.

In experienced hands, surgery, either alone or in combination with radiotherapy, effects a cure in around 60% of patients, although in less than half with macroadenomas (the majority of patients with acromegaly),^{1, 2} and remains first-line therapy. For those who require medical therapy, dopamine agonists have limited efficacy.^{1, 2} However, SMS analogues, which normalise IGF-I levels in about a half to two-thirds of acromegalic patients, normalise GH levels (long-acting formulations) in around 50% of patients and may be associated with tumour size reduction (in about 30% of patients,² are a second-line option for those who respond to them. The availability of the long-acting formulations allows 4-weekly administration. Pegvisomant is a third-line option for patients in whom surgery and/or radiotherapy and conventional medical therapy have been unable to effect a cure/remission or in those unable to tolerate or who are unresponsive to dopamine agonists or SMS analogues.

A 42-week, open-label, dose-finding study, published as a research letter, concluded that combined treatment with monthly high-dose long acting SMS analogue therapy and weekly SC pegvisomant is as effective as daily pegvisomant.¹³ The authors noted that pegvisomant monotherapy once daily leads to normal IGF-I concentrations in most patients with acromegaly, but is very costly. The starting dose of pegvisomant was 25 mg per week. It was adjusted until serum IGF-I concentrations were within the age-adjusted normal range or until a weekly dose of 80 mg was reached. Monthly treatment with long-acting SMS analogues was continued. IGF-I reached normal concentrations in 18 of 19 (95%) patients who completed 42 weeks of treatment with a median weekly dose of 60 mg pegvisomant (range 40-80 mg). However, pegvisomant is not licensed to be used in this way.⁶

Lifelong treatment with pegvisomant would be required to maintain IGF-I levels within the age-adjusted normal range, which is associated with a reduction in the excess mortality and morbidity associated with acromegaly. It should be noted that, to date, efficacy data is only available from one 12-week controlled trial and the duration of the currently available published safety data is only up to 18 months.

ARRANGEMENTS FOR PRESCRIBING

Pegvisomant should only be initiated by tertiary care specialists experienced in the full range of treatment modalities available for acromegaly. Its prescribing should remain within secondary care until more experience of its use is available. It will be indicated in a small minority of patients, such as the most extreme cases and those intolerant of or unwilling to undertake other treatments.¹⁶ Consideration should be given to limiting its use to one or a few centres to maximise experience. Limiting use would facilitate the collection and monitoring of data and outcomes in patients treated with pegvisomant.

FUTURE DEVELOPMENTS

Due to the rare nature of acromegaly and the relatively short duration of the clinical effectiveness and safety trials, it is necessary for clinicians to report all adverse reactions to pegvisomant.

Trials investigating the effects of long-term pegvisomant treatment are required, particularly to establish whether continually raised GH concentrations affect tumour growth.

ACKNOWLEDGEMENTS

We are grateful to the following people for helpful advice and comments in the preparation of this report. The Regional Drug and Therapeutics Centre accepts final responsibility for the content of this document.

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APPENDICES

APPENDIX I: SUMMARY OF TRIALS

Key: A/E – adverse effect; ALT – alanine aminotransferase; AST – aspartate transaminase; DB – double blind; C – controlled; CRP: C-reactive protein; CrS – cross-sectional; CT – computed tomography; DM – diabetes mellitus; F/U – follow-up; HDL-C – high-density lipoprotein cholesterol; Hom – homocysteine; IGF-I – insulin-like growth factor I; IL-6 – Interleukin-6; LDL-C-low density lipoprotein cholesterol; Lip – lipoprotein(a); max – maximum; MC - multicentre; MRI – magnetic resonance imaging, mths – months; n – number in group; NTx-cross-linked N-telopeptides of type I collagen; O - open; Obs – Observational; OD – once daily; Pbo – placebo-controlled; PICP- carboxyterminal propeptide of type I procollagen; PVT – Pegvisomant, Prl – parallel; pts – patients; R - randomised; SC - single centre; s/c - subcutaneous; SMS – somatostatin; TC- total cholesterol; TG –Triglycerides; UC – uncontrolled; yrs - years

Summary of main clinical trials

Reference	Design	Intervention	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Trainer et al 2000 ¹	12-week R, DB, Pbo, MC	s/c 80 mg PVT loading dose then PVT 10 mg OD n=26. s/c 80 mg PVT loading dose then PVT 15 mg OD n=26. s/c 80 mg PVT loading dose then PVT 20 mg OD n=28. s/c placebo loading dose and then placebo OD n=31.	Acromegaly established by signs and symptoms and pituitary adenoma shown by CT or MRI of pituitary fossa, plus IGF-I levels ≥ 1.3 times upper limit of age-adjusted normal range, >18 yrs old. SMS analogues and dopamine agonists discontinued.	Treatment with long-acting SMS analogue within 12 weeks before enrolment.	Percentage change in serum IGF-I concentration from baseline.	Percentage changes in serum IGF-I from baseline were: -26.7%, -50.1%, -62.5% and -4.0% in the PVT 10-mg, 15-mg, 20-mg and placebo groups, respectively (all p<0.001 vs. placebo).	4 patients withdrew, 2 for persistent headache, 1 due to large tumour and 1 with raised aminotransferase levels.

Reference	Design	Intervention	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
van der Lely et al 2001 ⁷	18-month, O, MC, UC, Obs	s/c PVT 10 mg OD titrated up or down in 5-mg increments until normalisation of IGF-I or max dose of 40 mg OD. Mean doses were 14.7 mg, 18.0 mg and 19.6 mg per day for 6-, 12- and 18-month cohorts, respectively. N=152, 131 pts treated for 6 months, 90 for 12 months and 39 for 18 months, (160 pts entered safety analysis).	Acromegaly plus IGF-I levels ≥ 1.3 times upper limit of age-adjusted normal range at least 2 weeks after discontinuation of short-acting SMS analogues and 5 weeks after discontinuation of dopamine agonists, > 18yrs old.	None stated	1) Change in tumour volume assessed by MRI 2) Change in serum GH concentration 3) Change in serum IGF-I concentration	1) Mean pituitary tumour volume did not decrease significantly (2.41 cm ³ at baseline to 2.37 cm ³ p=0.353) 2) Mean serum GH concentration increased by 12.5, 12.5 and 14.2 microgram/l for 6-, 12- and 18-month cohorts, respectively (p<0.05 for within-cohort baseline vs. final comparison). 3) Normal serum IGF-I concentration achieved in 97% of pts treated for ≥ 12 months. No other specific figures presented.	30 pts withdrew: 2 - protocol violations; 9 - adverse events; 5 - lack of efficacy; 2 - lost to F/U and 12 - voluntary. Anti-PVT antibodies seen in 16.9% of patients. Anti-GH antibodies seen in 16 patients. No tachyphylaxis seen. 2 pts had growth of pituitary tumours. 2 pts had increases in ALT and AST > 10 times upper limit of normal.

The use of pegvisomant in the management of acromegaly

Reference	Design	Intervention	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Sesnilo 2002 ⁹	(Part 1) MC, C1S	Active acromegaly after wash out from current medical therapy, n=48	Active acromegaly diagnosed according to standard clinical and biochemical criteria (confirmed pituitary adenoma by imaging) plus IGF-I levels $\geq 30\%$ above upper limit of age-adjusted upper limit of normal range ≥ 2 weeks after discontinuation of short-acting SMS analogues, ≥ 12 weeks after discontinuation of long-acting SMS analogues and ≥ 5 weeks after discontinuation of dopamine agonists.	None stated	CRP, IL-6, Insulin, TG, TC, Lip, LDL-C, HDL-C, Hom	CRP 0.3 mg/l vs. 2.0 mg/l in control ($p < 0.0001$); insulin 78.6 pM vs. 54.5 pM in control ($p = 0.0051$); IL-6 and Hom levels were similar among groups. No difference between groups for TG, TC, Lip, LDL-C, HDL-C.	Not reported
	(Part 2) 12-week R, DB, Pbo, MC longitudinal at post hoc analysis	Placebo (n=14), 10 mg PVT (n=12), 15 mg PVT (n=10) or 20 mg PVT (n=12).			<p><i>Post hoc</i> analysis of mean changes from baseline in levels of:</p> <p>CRP, IL-6, Insulin, TG, TC, Lip, LDL-C, HDL-C, Hom, GH, glucose</p>	<p>83% of PVT 20-mg group had normalised IGF-I levels.</p> <p>CRP 13.7 mg/l in PVT 20-mg group vs. 0.5 mg/l in placebo group ($p = 0.010$); GH 11.2 microgram/l in PVT 20-mg group vs. 0.0 microgram/l in placebo group ($p = 0.0013$)</p> <p>No differences between PVT 20-mg and placebo group values for TG, TC, Lip, LDL-C, HDL-C, Hom, IL-6, insulin, glucose.</p>	

The use of pegvisomant in the management of acromegaly

	<p>(Part 3) UC, F/U, longitudinal at open-label, study up to 18 months, <i>post hoc</i> analysis, including patients from part 2</p>	<p>All 48 pts given PVT 10 mg OD initially and adjusted in 5-mg increments at 8-week intervals to max 35 mg/day or until normalisation of IGF-I to age- and gender-specific normal range. Due to shortage of PVT, random withdrawals were made.</p>		<p><i>Post hoc</i> analysis of mean changes from baseline in levels of: CRP, IL-6, Insulin, TG, TC, Lip, LDL-C, HDL-C, Hom, GH, glucose, IGF-I</p>	<p>Analysis only on patients who achieved normal IGF-I levels (n=34) rather than intention-to-treat. CRP increased by 2.0+/- 0.5 mg/l (p=0.0002); TC increased by 0.22 mM (p=0.05); TG increased by 0.25 mM (p=0.007); GH increased by 13.4 microgram/l (p<0.0001) IGF-I decreased by 53Mm (P<0.0001) Changes in all other parameters were non-significant.</p>	
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Reference	Design	Intervention	Inclusion criteria	Exclusion Criteria	Primary Outcome	Results	Adverse Effects
Fairfield et al 2002 ¹⁰	MC, 12-week, Pbo, MC	<p>s/c 80 mg PVT loading dose then PVT 10 mg OD (n=7).</p> <p>s/c 80 mg PVT loading dose then PVT 15 mg OD (n=6).</p> <p>s/c 80 mg PVT loading dose then PVT 20 mg OD (n=7).</p> <p>s/c placebo loading dose then placebo OD (n=7).</p>	<p>Acromegaly established by clinical signs and symptoms and pituitary adenoma demonstrated by CT or MRI of pituitary fossa, plus IGF-1 levels ≥ 1.3 times upper limit of age and sex specific adjusted normal range, >18yrs old.</p> <p>SMS analogues and dopamine agonists discontinued as in other trials detailed.</p>	<p>Conditions that elevated GH and/or IGF-1 levels or used any medication that could interfere with study results.</p>	<p>Serum markers of bone formation: osteocalcin, PICP.</p> <p>Serum markers of bone resorption : NTx,</p>	<p>Serum osteocalcin level decreased significantly in combined PVT group (-2.20 nmol/l) vs. placebo (+0.01 nmol/l, p=0.009). PICP level decreased significantly in combined PVT group (-23.6 mcg/l) vs. to placebo (+18.1 microgram/l, p=0.022).</p> <p>NTx decreased significantly in combined PVT group (-4.4 nmol/l/l) vs. placebo (+1.0 nmol/l, p=0.024).</p>	