Provisional chapter

Pegvisomant in Acromegaly and Gigantism

Claire Briet, Valentine Suteau and Patrice Rodien

Additional information is available at the end of the chapter

Abstract

Pegvisomant is a GH antagonist used in acromegaly in gigantism. Pegvisomant is a modified GH molecule with pegylation to increase half-life and nine amino acid substitutions to modify GH receptor affinity and dimerization. Pegvisomant leads to an IGF1 decrease. It is administered subcutaneously every day with a median dose of 15 mg/day in meta-analysis. This treatment is indicated in acromegaly or gigantism in case of resistance to somatostatin analogs. This drug leads to a control of acromegaly in 90% of patients in phase III study and about 70% of patients in real-life study. In gigantism, only 50% of children are controlled with pegvisomant. It is a well-tolerated treatment with hepatic side effects in 3% of cases, headache in 2% of cases, and lipohypertrophy in 3% of cases. Pegvisomant does not act on adenoma size, and 6% of increasing tumour size is observed. Indeed, pegvisomant is an antagonist of GH receptor with a good efficacy which can be used alone or in association with somatostatin analog or cabergoline if acromegaly is not controlled by a somatostatin analog.

Keywords: acromegaly, gigantism, pegvisomant

1. Introduction

Pegvisomant is the only available GH antagonist. The history of pegvisomant development is an example of how research can be surprising. By combining site-specific mutation on the GH gene, researchers were looking for a long-acting GH treatment. However, researchers were surprised to find with the in vivo analysis an IGF1 reduction in mice treated with the modified GH molecule obtained. It was the beginning of pegvisomant history.

2. Structure-function

2.1. Development of a long-acting GH antagonist

GH three-dimensional structure contains two disulphide bridges and four helices which are arranged in an "up-up-down-down" topology. Helices 1, 2, 3, and 4 are located between residues 9–34, 72–92, 106–128, and 155–184, respectively (**Figure 1**) [1]. Helix 3 is the key to promote a growth activity. In this helix, approximately 20 amino acids are arranged in an amphiphilic orientation. Among them, three amino acids do not enable an ideal amphiphilic helix [2]. When modifying these three amino acids, researchers wanted to generate a perfect amphiphilic helix 3 and hypothesised that it would enhance GH activity. Surprisingly, transgenic mice expressing this modified GH analog had decreased circulating IGF1 concentrations. It was the first report of a GH antagonist [3]. Further single amino acid substitutions demonstrated that glycine at position 120 of human GH was critical for the growth-promoting activity of the respective molecule. Crystallography studies demonstrated that this mutation of the glycine to a lysine at position 120 (G120K) of GH led to a defect of GHR dimerisation which is essential for GH transduction signal [4].

However, because of its small size (22 kDa), GH is rapidly cleared by the kidneys and/or endocytosis as a GH/GHR complex. Indeed, the addition of polyethylene glycol (PEG) (5 kDa)

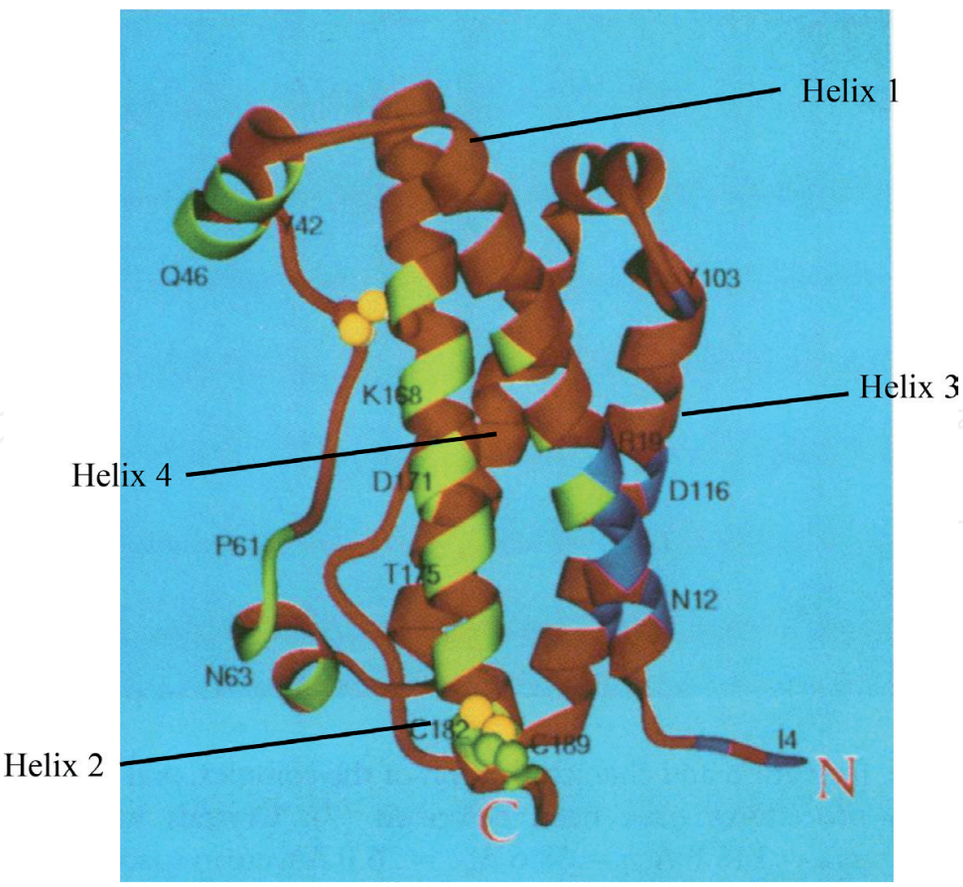

Figure 1. Two-dimensional representation of the structure of human GH (adapted from de Vos et al.) [4].

increased the serum half-life from 30 min to 2 days. At this stage, we had a G120K-PEG GH molecule. However, the perfect GH antagonist was not yet found because the addition of PEG led to a decrease of binding affinity for site 1 (which is the first binding site of the GH molecule on the GH receptor). To circumvent this problem, mutagenesis of binding site 1 was considered. In the meantime, Cunningham and Wells published a more potent GH analog with eight amino acid substitutions in site 1 of the GH molecule. These eight mutations were introduced in the G120K-PEG GH molecule [5]. This molecule proved to maintain binding affinity for binding site 1 of GHR, antagonising properties of GHR with a long half-life. That was the birth of pegvisomant.

2.2. The pegvisomant/GHR interaction

Pegvisomant/GHR interaction has been more precisely studied. Primary studies suggest that pegvisomant binds to one GHR and prevents GHR dimerisation because of the G120K mutation which prevents binding to site 2. However, further studies show that pegvisomant

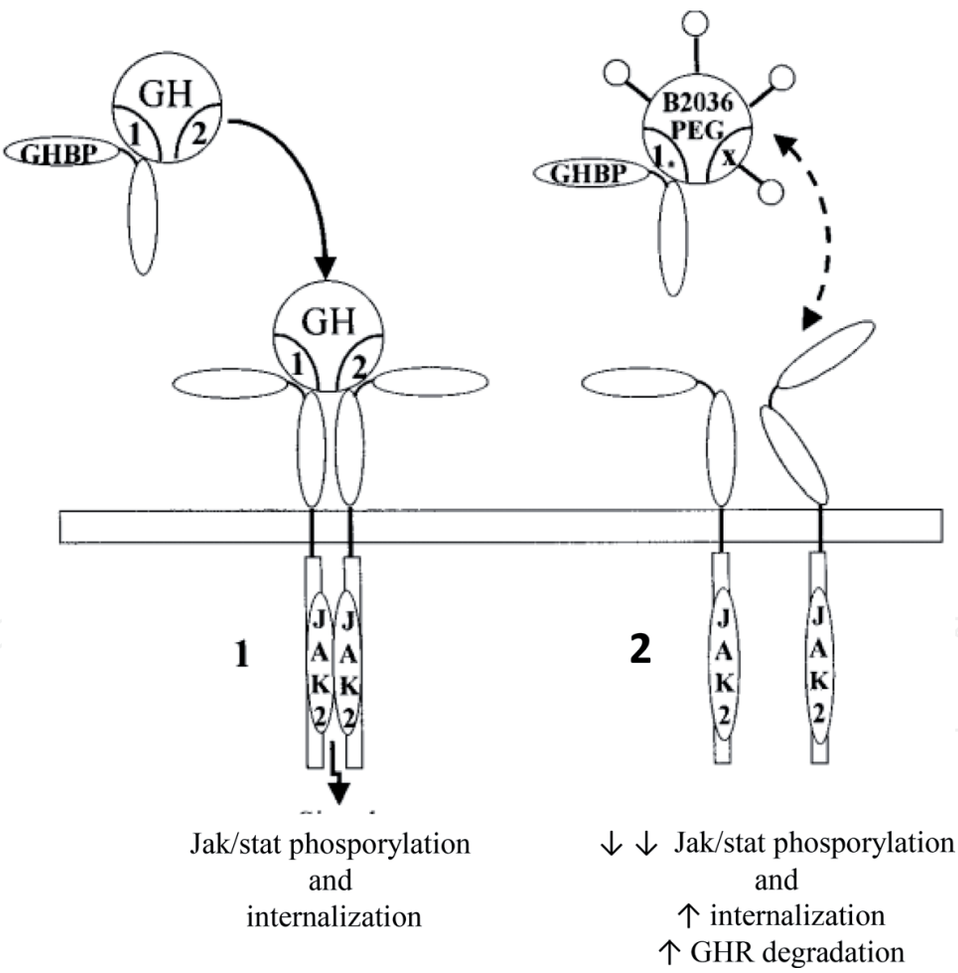

Figure 2. Binding representation of GH and pegvisomant (B2036-PEG) on GH receptor and schematic effect [1]. GH binds to GHBP and to binding site 1 and 2, inducing a conformational change of GHR, a jak/stat phosphorylation, and internalisation [2]. Pegvisomant binds to GHBP, and the complex binds to site 1 and site 2, inducing a less functional dimerization, a diminution of jak/stat phosphorylation, and a different intracellular trafficking with an increase of GH receptor degradation (adapted from Ross et al.) [6].

induces GHR dimerisation with disulphide linkage and induces internalisation, as GH do. However, activation of jak kinase and stat 5 is less important because the conformation changes after pegvisomant binding is different with a less functional dimerisation [6, 7]. Moreover, internalisation after pegvisomant binding induces a different intracellular trafficking, with an increase of degradation of GHR, a decrease of GHR expression on cellular membrane, and a decrease of nuclear localisation of GHR [8].

Moreover, it appears that the eight mutations within site 1 do not increase affinity to GHR but to the GH binding protein and allow the dimerisation of GHR despite the pegylation (**Figure 2**) [7]. Reducing site 1 binding affinity, high doses of pegvisomant are necessary to antagonise GH action.

3. Safety-efficacy

3.1. Phase I

In the phase I study, 36 young volunteers received a single injection of either the placebo or pegvisomant (0.03, 0.1, 0.3, or 1.0 mg/kg). All doses were well tolerated, with no severe adverse events. IGF1 decreased significantly in all groups with a pegvisomant dose above 0.1 mg/kg ($P < 0.001$ vs. placebo) [9].

3.2. Phase II

In the phase II study, 46 patients with active acromegaly were randomised and received the placebo, 30 or 80 mg of pegvisomant once a week for 6 weeks. If IGF1 levels were unchanged in the placebo group, it decreased by 31 ± 6.7% in the 80 mg groups ($P < 0.001$). There was a dose-related decrease in serum IGF1. However, only three patients have a normal serum IGF1. Pharmacokinetic study evaluated pegvisomant half-life at 70 h [10]. Because of the low efficacy of pegvisomant in phase II and the half-life of 70 h, it was decided to give pegvisomant daily in phase III.

3.3. Phase III

The phase III study on 112 patients with acromegaly showed the efficacy of pegvisomant on serum IGF1 reduction and clinical improvement. This double-blind study showed a decrease of IGF1 from the baseline by 26.7 ± 27.9%, 50.1 ± 26.7%, and 62.5 ± 21.3% in the groups that received 10 mg, 15 mg, and 20 mg of pegvisomant per day, respectively ($P < 0.001$ for the comparison of each pegvisomant group with placebo). In these groups, 54%, 81%, and 89% had a normalised IGF1 at 12 weeks. Among patients treated with 15 mg or 20 mg of pegvisomant per day, there were significant decreases in clinical symptoms such as ring size, soft tissue swelling, the degree of excessive perspiration, and fatigue. Quality of life improved in all groups. Tumour volume was similar before pegvisomant and at 12 weeks [11]. One year later, van der Lely et al. published the extension of this study, with 152 patients on pegvisomant at 18 months; 97% of patient normalised serum IGF1 (**Table 1**) [12].

	N (female)	IGF1 before pegvisomant % ULN	Median exposure time (months)	Median dose mg/day (min max)	Monotherapy (% of patients)	Normal IGF1 (% of patients)	Tumour enlargement (% of patients)	Liver enzyme elevation (% of patients)
Boguszewski et al. [14]	109 (61)	209 (99–637)	30.5	10 (10–30)	11	74.1%	6	9.2
Basavilbaso et al. [33]	75 (51)	240 (125–700)	27	12 (3–30)	45	63%	9.8	9.3
Buchfelder et al. [13]	2090	NA	91.2	18.9	NA	73	2.2	3
Van der Lely et al. [12]	90	NA	18	19.6	100	97	1.3	1.3
Garcia et al. [18]	42	NA	NA	NA	NA	58	NA	NA
Rostomyan et al. [19]	37	NA	NA	NA	NA	51	NA	NA

NA: not available; ULN: Upper limit normal.

Table 1. Main study of pegvisomant efficacy and adverse events in real life.

3.4. Long-term experience

3.4.1. Efficacy

The ACROSTUDY is the largest international, noninterventional study of acromegaly patients treated by pegvisomant. Two thousand and ninety patients were analysed between 2004 and 2016. When starting pegvisomant, 89% of patients had an IGF1 above the upper limit of normal (ULN), previously treated by surgery, radiotherapy, medical therapy, or a combination of the three. After 10 years, 73% of patients had a normal IGF1 with a median dose of pegvisomant 18.9 mg/day (**Table 1**) [13].

A recent study evaluated the efficacy in real life. A Brazilian multicentre study of 109 patients with acromegaly were included, 61% were women, and 95% have macroadenomas. Previous treatments were surgery (89%), radiotherapy (34%), somatostatin analogs (99%), and/or cabergoline (67%). No patients were controlled at inclusion with high IGF1 (median 209% of ULN) and high GH secretion. For most patients the initial dose was 10 mg/day, and the median exposure was 30.5 months. Pegvisomant was used as monotherapy in 11%. IGF1 normalisation was obtained in 74% of patients with a median dose of 15 mg/day when used alone and 10 mg/day in combined therapy. In this study, there were three response predictors: exposure time, GH pretreatment, and IGF1 pretreatment (**Table 1**) [14].

In a recent meta-analysis of eight studies, 60.9% of patients were controlled (52–70; 95% CI) and 72% if considering only patients in monotherapy in five studies [15].

Interestingly, there are two cases of persistent remission of acromegaly after pegvisomant withdrawal. Patients were treated for 8 and 11 years and presented a normal IGF1 and GH secretion 5 and 2 years after withdrawal, respectively [16].

3.4.2. Adherence

In a recent study, treatment adherence to pegvisomant was evaluated in a multicentre cross-sectional study on patients treated with pegvisomant for more than 12 months in 108 patients. Rates of adherence varied from 61 to 92% and did not correlate to disease control. Older patients and patients with an alternative schedule had lower adherence. However, treatment satisfaction was high, 75 ± 15%, evaluated with the "Treatment Satisfaction with Medicines Questionnaire" (STATMED-Q). This study reveals that the principal obstacle was the transportation of the pegvisomant (especially maintaining the cold chain during transportation) and anxiety about the injection. One third of patients made mistakes during the reconstitution (17%) and administration (22%) of pegvisomant [17].

3.5. Experience of pegvisomant in children

Experience of pegvisomant in children is quite rare. There is a recent review of the case series of gigantism in the literature. Out of 262 patients, 42 (17.5%) were treated with pegvisomant and 27 (58%) had normal IGF1 [18]. The biggest series was published in 2015 with 208 patients with gigantism. Among them 37 were treated with pegvisomant and 19/37 (51%) had a normal IGF1. Indeed, gigantism seems to be more difficult to control than acromegaly in adulthood with pegvisomant [19].

4. Indication

4.1. Acromegaly patients

Endocrine society guidelines for acromegaly were published in 2014 [20]. The first recommended treatment of acromegaly is surgery, as it offers the prospect of a cure. In case of persistent GH secretion 12 weeks after surgery, medical treatment is indicated including cabergoline and long-acting somatostatin (SMS) analogs. Cabergoline is indicated in case of co-secretion of GH and PRL or if GH secretion is slightly increased (IGF1 < 2.5 times the upper normal range) and permits 40–50% of control [21, 22]. The first generation of long-acting SMS analog studies report around 50% of IGF1 normalisation [23]. For patients who are not controlled by the first-generation SMS analogs, the recent consensus recommends several options:

Add cabergoline if IGF1 is <2.5 times the upper normal range.

Switch to pasireotide, the second-generation of SMS analogs which normalised IGF1 in up to 54% of patients [24].

Switch or add pegvisomant [25].

Pegvisomant is indicated in cases of resistance to SMS analog in a second- or third-line therapy [20]. In addition, pegvisomant should be considered in patient with uncontrolled diabetes with partial or no response to first-line medical therapy [25].

4.2. Posology

For the first dose, 80 mg is recommended, followed by 10 mg/day. IGF1 should be measured 8 weeks after, and pegvisomant should be increased by stages of 5 mg.

The dose of pegvisomant required to normalise IGF1 can be evaluated with age and BMI; however, it is recommended to monitor IGF1 in order to adapt pegvisomant dosage. Using dose above 30 mg/day is not recommended [26].

4.3. Combination therapy

When patients are not controlled with somatostatin analog ± cabergoline, the question of adding pegvisomant or switching to pegvisomant is not yet resolved. Initially, with serum IGF1 normalisation in over 90% of patients with acromegaly receiving pegvisomant, the indications for combined therapy were limited. However, in real life, as efficacy is lower (almost 70%), the combination therapy is questionable. Moreover, because of the risk of tumour growth and chiasma compression, the strategy for macroadenoma was often to add pegvisomant to somatostatin analog. However, the routine use of SMS analog and pegvisomant in combination may also be prohibitively expensive [27].

A randomised trial compared the two strategies for patients uncontrolled under long-acting octreotide: switched to pegvisomant alone or added pegvisomant. IGF1 normalisation was similar in both groups (56% for pegvisomant alone and 62% for combined therapy). The question still remains unanswered [28].

In a large Dutch cohort of patients with acromegaly treated with the association of somatostatin analog and pegvisomant for 9 years, 97% of patients had a normal IGF1 with a median dose of pegvisomant of 80 mg/week [29].

Moreover, the association of cabergoline and pegvisomant for patients with a slightly increase of IGF1 under pegvisomant alone for 18 months enabled acromegaly control in four patients (28%) [22].

4.4. Monitoring and objectives

IGF1 is the only biological marker to evaluate disease activity on pegvisomant. As it is a GH antagonist, it is not recommended to follow GH secretion. Indeed, scoring systems have been developed to evaluate the activity of acromegaly. In this way, SAGIT and ACRODAT are additional tools to assess overall disease activity [30, 31]. AcroQol can be useful to evaluate the quality of life of acromegaly patient under treatment [32].

5. Adverse events

5.1. Hepatic

In the phase III study, one patient with 15 mg/day of pegvisomant withdrew after 8 weeks of therapy because of elevated serum aminotransferase levels, with a normalisation of liver

function after withdrawal. In this patient, serum alanine aminotransferase and aspartate aminotransferase rose to 20 N and 10 N, respectively. In the cohort of patients receiving pegvisomant, mean serum aminotransferase levels were stable (n = 80) [11].

In the Brazilian and Argentinian cohort, elevation of liver enzymes was reported in 9% of cases and was responsible for pegvisomant discontinuation in 1 and 5 patients, respectively (**Table 1**) [14, 33].

A recent meta-analysis of 6 studies with pegvisomant in monotherapy showed an overall rate of transaminase elevation of 3.0% (1.7–5.2%; 95% CI; I 2 = 55%) (**Table 1**) [15].

5.2. Headache

In the phase III study, one patient with 15 mg/day of pegvisomant withdrew due to persistent headaches [11]. In the Brazilian real-life study, headaches were reported in two cases (1.8%) [14].

5.3. Cutaneous lipohypertrophy

In the phase III study, injection site reactions were reported in six patients (5%) receiving pegvisomant [11]. In the Brazilian real-life study, it was reported in 4.6% of patients [14]. Pain from injection was reported in 2.7% patients.

In the Argentinian cohort, 3 out of 75 patients had localised lipodystrophy [33].

A recent meta-analysis of five studies with pegvisomant showed lipohypertrophy in 1.6% of patients (0.6–4.3%; 95% CI; I 2 = 69%) [15].

5.4. Antibody formation

Because of the nine amino acid substitutions, pegvisomant is different from GH and can be considered as foreign protein leading to an immunoreactivity. Pegylation of the molecule reduces immunogenicity. However, in the phase III study and its extension, anti-GH antibodies were reported in 8/112 (7%) patients between 1:14 and 1:64 and pegvisomant antibody in 16.9% [12, 15].

5.5. Metabolic

Several studies evaluated glucose metabolism in patients with pegvisomant. In 53 patients initially treated by long-acting octreotide, the switch for pegvisomant treatment induced normalisation of IGF1 in 78% of cases at 32 weeks and a significant diminution of median fasting glucose (1.4 mmol/l) and HbA1C (−0.2%) whatever the diabetes and IGF1 status. In the subgroup of diabetic patients, a significant decrease of HbA1C (−1%) was observed [34].

In the ACROSTUDY, among the 1762 patients, 29% had diabetes before pegvisomant. At year 4, mean fasting blood glucose decreased from 140 ± 59 to 120 ± 44 mg/dl, and the decrease of HbA1C was not significant whatever the diabetes status [35].

In a recent meta-analysis, pegvisomant significantly decreased fasting blood glucose level (−0.8 mmol/l; 95% CI; −1.0 to −0.6), fasting insulin level (−5.31; 95% CI; −10.2 to −0.4), and

HbA1c (−0.43%; 95% CI; −0.6 to −0.3). Indeed, HOMA-I also decreased −0.61 (95% CI; −1.2 to −0.04). This increase in glucose metabolism was not correlated to IGF1 level [36].

5.6. Tumour size

In the ACROSTUDY, subjects received pegvisomant for a mean of 5.4 years, and 12 out of 542 subjects (2.2%) had a confirmed increase in tumour size (**Table 1**) [37].

In the Brazilian study, tumour enlargement was reported in 6.5% of cases (n = 5). In the Argentinian study, 4 of 50 patients (8%) showed an increase in tumour size with pegvisomant (**Table 1**) [33]. In the meta-analysis of five studies with pegvisomant in monotherapy, the overall tumour growth rate was 7.2% (4.8–10.7%; 95% CI; I 2 = 0%) [15].

5.7. Bones

The bone is a well-known fragility key point in acromegaly with a high incidence of vertebral fractures [38]. A recent study evaluated vertebral fracture in 55 patients resistant to the first generation of somatostatin analogs. Before introducing pasireotide or pegvisomant, vertebral fracture occurred in 23 patients (42%). In uncontrolled acromegaly, there were 78% of vertebral fractures under pegvisomant and 25% under pasireotide (p = 0.04). In controlled acromegaly, there were 23% of vertebral fractures under pegvisomant and 12.5% under pasireotide (p = 0.4). Indeed, vertebral fractures seem to be more frequent with pegvisomant [39].

However, another longitudinal study has a different result in 83 patients treated with somatostatin analog alone (42 cases), pegvisomant alone (6 cases), or in combination with somatostatin analog (35 cases) for a median period of 82 months (range 36–126). In this longitudinal study, the authors observed a global decrease in incidence of radiological vertebral fractures from 43.9 to 26.8% (p = 0.039). For patients treated by pegvisomant, the incidence of vertebral fractures was not significantly decreased as compared to patients treated with somatostatin analog (10.0 vs. 26.7%; p = 0.09). In this study, pegvisomant did not increase vertebral fractures [40].

6. Conclusion

Pegvisomant is an antagonist of GH receptor with a good efficacy. It can be used alone or in association with somatostatin analog or cabergoline if acromegaly is not controlled with somatostatin analog alone. The efficacy in real life is around 75% in acromegaly and 50% for gigantism. Indeed, pegvisomant can be used in the second medical stage after somatostatin analog.

Author details

Claire Briet*, Valentine Suteau and Patrice Rodien

*Address all correspondence to: claire.briet@chu-angers.fr

Endocrinology, Diabetology and Nutrition Department, INSERM U1083, Institut Mitovasc, CHU, Angers, France

References

[1] Abdel-Meguid SS, Shieh HS, Smith WW, Dayringer HE, Violand BN, Bentle LA. Three-dimensional structure of a genetically engineered variant of porcine growth hormone. Proceedings of the National Academy of Sciences of the United States of America. 1987;**84**:6434-6437

[2] Hara K, Hsu Chen CJ, Sonenberg M. Recombination of the biologically active peptides from a tryptic digest of bovine growth hormone. Biochemistry. 1978;**17**:550-556

[3] Chen WY, Wight DC, Wagner TE, Kopchick JJ. Expression of a mutated bovine growth hormone gene suppresses growth of transgenic mice. Proceedings of the National Academy of Sciences of the United States of America. 1990;**87**:5061-5065

[4] de Vos AM, Ultsch M, Kossiakoff AA. Human growth hormone and extracellular domain of its receptor: Crystal structure of the complex. Science. 1992;**255**:306-312

[5] Cunningham BC, Wells JA. Rational design of receptor-specific variants of human growth hormone. Proceedings of the National Academy of Sciences of the United States of America. 1991;**88**:3407-3411

[6] Ross RJ, Leung KC, Maamra M, Bennett W, Doyle N, Waters MJ, et al. Binding and functional studies with the growth hormone receptor antagonist, B2036-PEG (pegvisomant), reveal effects of pegylation and evidence that it binds to a receptor dimer. The Journal of Clinical Endocrinology and Metabolism. 2001;**86**:1716-1723

[7] Yang N, Langenheim JF, Wang X, Jiang J, Chen WY, Frank SJ. Activation of growth hormone receptors by growth hormone and growth hormone antagonist dimers: Insights into receptor triggering. Molecular Endocrinology. 2008;**22**:978-988

[8] Lan H, Li W, Li R, Zheng X, Luo G. Endocytosis and degradation of Pegvisomant and a potential new mechanism that inhibits the nuclear translocation of GHR. The Journal of Clinical Endocrinology and Metabolism. 2019;**104**:1887-1899

[9] Thorner MO, Strasburger CJ, Wu Z, Straume M, Bidlingmaier M, Pezzoli SS, et al. Growth hormone (GH) receptor blockade with a PEG-modified GH (B2036-PEG) lowers serum insulin-like growth factor-I but does not acutely stimulate serum GH. The Journal of Clinical Endocrinology and Metabolism. 1999;**84**:2098-2103

[10] van der Lely AJ, Lamberts S, Barkan A, Panadya N, Besser GM, Trainer PJ, et al. A six week, double blind, placebo controlled study of a growth hormone antagonist, B2036-PEG (Trovert) in acromegalic patients. In: Program of the 80th Annual Meeting of the Endocrine Society, New Orleans, LA. 1998. p. 57

[11] Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. The New England Journal of Medicine. 2000;**342**:1171-1177

[12] van der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, et al. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet. 2001;**358**:1754-1759

[13] Buchfelder M, van der Lely AJ, Biller BMK, Webb SM, Brue T, Strasburger CJ, et al. Long-term treatment with pegvisomant: Observations from 2090 acromegaly patients in ACROSTUDY. European Journal of Endocrinology. 2018;**179**:419-427

[14] Boguszewski CL, Huayllas MKP, Vilar L, Naves LA, Ribeiro-Oliveira Junior A, Soares BS, et al. Brazilian multicenter study on pegvisomant treatment in acromegaly. Archives of Endocrinology and Metabolism. 2019;**63**:328-336

[15] Leonart LP, Tonin FS, Ferreira VL, Fernandez-Llimos F, Pontarolo R. Effectiveness and safety of pegvisomant: A systematic review and meta-analysis of observational longitudinal studies. Endocrine. 2019;**63**:18-26

[16] Puglisi S, Spagnolo F, Ragonese M, Cannavo S, Ferrau F. First report on persistent remission of acromegaly after withdrawal of long-term pegvisomant monotherapy. Growth Hormone & IGF Research. 2019;**45**:17-19

[17] Camara R, Venegas E, Garcia-Arnes JA, Cordido F, Aller J, Samaniego ML, et al. Treatment adherence to pegvisomant in patients with acromegaly in Spain: PEGASO study. Pituitary. 2019;**22**:137-145

[18] Garcia WR, Cortes HT, Romero AF. Pituitary gigantism: A case series from hospital de San Jose (Bogota, Colombia). Archives of Endocrinology and Metabolism. 2019;**63**:385-393

[19] Rostomyan L, Daly AF, Petrossians P, Nachev E, Lila AR, et al. Beckers A 2015 Clinical and genetic characterization of pituitary gigantism: An international collaborative study in 208 patients. Endocrine-Related Cancer 22:745-757

[20] Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: An endocrine society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism. 2014;**99**:3933-3951

[21] Sandret L, Maison P, Chanson P. Place of cabergoline in acromegaly: A meta-analysis. The Journal of Clinical Endocrinology and Metabolism. 2011;**96**:1327-1335

[22] Kuhn E, Chanson P. Cabergoline in acromegaly. Pituitary. 2017;**20**:121-128

[23] Lamberts SWJ, Hofland LJ. Anniversary review: Octreotide, 40 years later. European Journal of Endocrinology. 2019;**181**:R173-R183

[24] Shimon I, Adnan Z, Gorshtein A, Baraf L, Saba Khazen N, Gershinsky M, et al. Efficacy and safety of long-acting pasireotide in patients with somatostatin-resistant acromegaly: A multicenter study. Endocrine. 2018;**62**:448-455

[25] Giustina A, Barkan A, Beckers A, Biermasz N, Biller BMK, Boguszewski C, et al. A consensus on the diagnosis and treatment of acromegaly comorbidities: An update. The Journal of Clinical Endocrinology and Metabolism. 2019

[26] Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JAH, et al. A consensus statement on acromegaly therapeutic outcomes. Nature Reviews. Endocrinology. 2018;**14**:552-561

[27] Elbaum M, Mizera L, Bolanowski M. The real costs of acromegaly: Analysis of different therapies. Endokrynologia Polska. 2019;**70**:74-85

[28] Trainer PJ, Ezzat S, D'Souza GA, Layton G, Strasburger CJ. A randomized, controlled, multicentre trial comparing pegvisomant alone with combination therapy of pegvisomant and long-acting octreotide in patients with acromegaly. Clinical Endocrinology. 2009;**71**:549-557

[29] Neggers SJ, Franck SE, de Rooij FW, Dallenga AH, Poublon RM, Feelders RA, et al. Long-term efficacy and safety of pegvisomant in combination with long-acting somatostatin analogs in acromegaly. The Journal of Clinical Endocrinology and Metabolism. 2014;**99**:3644-3652

[30] Giustina A, Bevan JS, Bronstein MD, Casanueva FF, Chanson P, Petersenn S, et al. SAGIT(R): Clinician-reported outcome instrument for managing acromegaly in clinical practice-development and results from a pilot study. Pituitary. 2016;**19**:39-49

[31] van der Lely AJ, Gomez R, Pleil A, Badia X, Brue T, Buchfelder M, Burman P, Clemmons D, Ghigo E, Jorgensen JOL, Luger A, van der Lans-Bussemaker J, Webb SM, Strasburger CJ 2017 Development of ACRODAT((R)), a new software medical device to assess disease activity in patients with acromegaly. Pituitary 20:692-701

[32] Webb SM, Badia X, Surinach NL, Spanish AcroQol Study Group. Validity and clinical applicability of the acromegaly quality of life questionnaire, AcroQoL: A 6-month prospective study. European Journal of Endocrinology. 2006;**155**:269-277

[33] Basavilbaso NXG, Ballarino MC, Bruera D, Bruno OD, Chervin AB, Danilowicz K, et al. Pegvisomant in acromegaly: A multicenter real-life study in Argentina. Arch Endocrinol Metab. 2019;**63**:320-327

[34] Barkan AL, Burman P, Clemmons DR, Drake WM, Gagel RF, Harris PE, et al. Glucose homeostasis and safety in patients with acromegaly converted from long-acting octreotide to pegvisomant. The Journal of Clinical Endocrinology and Metabolism. 2005;**90**: 5684-5691

[35] Brue T, Lindberg A, Jan van der Lely A, Akerblad AC, Koltowska-Haggstrom M, Gomez R, et al. Diabetes in patients with acromegaly treated with pegvisomant: Observations from acrostudy. Endocrine. 2019;**63**:563-572

[36] Feola T, Cozzolino A, Simonelli I, Sbardella E, Pozza C, Giannetta E, et al. Pegvisomant improves glucose metabolism in acromegaly: A meta-analysis of prospective interventional studies. The Journal of Clinical Endocrinology and Metabolism. 2019;**104**:2892-2902

[37] Freda PU, Gordon MB, Kelepouris N, Jonsson P, Koltowska-Haggstrom M, van der Lely AJ. Long-term treatment with pegvisomant as monotherapy in patients with acromegaly: Experience from ACROSTUDY. Endocrine Practice. 2015;**21**:264-274

[38] Chiloiro S, Mormando M, Bianchi A, Giampietro A, Milardi D, Bima C, et al. Prevalence of morphometric vertebral fractures in "difficult" patients with acromegaly with different biochemical outcomes after multimodal treatment. Endocrine. 2018;**59**:449-453

[39] Chiloiro S, Antonella G, Frara S, Bima C, Donfrancesco F, Maya FC, et al. Effects of pegvisomant and pasireotide LAR on vertebral fractures in acromegaly resistant to

first-generation SRLs. Journal of Clinical Endocrinology and Metabolism. 2019. pii: dgz054

[40] Chiloiro S, Mazziotti G, Giampietro A, Bianchi A, Frara S, Mormando M, et al. Effects of pegvisomant and somatostatin receptor ligands on incidence of vertebral fractures in patients with acromegaly. Pituitary. 2018;**21**:302-308

IntechOpen

IntechOpen