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EDITORIAL

Pegvisomant: Balance after 10 years☆

Pegvisomant: balance de 10 años

Ignacio Bernabeu[a,*], **Mónica Marazuela**[b]

[a] *Servicio de Endocrinología y Nutrición, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, La Coruña, Spain*
[b] *Servicio de Endocrinología y Nutrición, Hospital Universitario de La Princesa, Madrid, Spain*

Pegvisomant (PEG) was approved by the European Medicines Agency in November 2002 for patients with persistent acromegaly after surgery not controlled with somatostatin analogs (SSAs). In Spain, PEG was marketed in 2004, more than a decade ago. This appears, therefore, to be a good time to discuss our experience with using the drug, to review the most recent data regarding its efficacy and safety, and to draw up recommendations for its more efficient use.

PEG is an analog of human growth hormone (GH) with nine amino acid substitutions in its molecule. One of these, the G120K substitution, confers on PEG its antagonistic effect. All other amino acid substitutions and subsequent combination with polyethylene glycol molecules maintain PEG affinity for the GH receptor (GHR), decrease its immunogenicity, and prolong its half-life.[1] PEG binds to GHR, preventing its activation and, thus, the effects of excess GH. This is a novel mechanism of action independent of the molecular characteristics of the tumor.

Until the advent of PEG, a significant proportion of patients with acromegaly continued to have active and progressive disease because of their poor response to the available treatments. Changes in treatment (high SSA doses, more frequent dosing, change in SSA, combinations with dopamine agonists) or high-risk repeat surgery or radiation therapy with low success rates were often used. The marketing of PEG represented a great hope for these patients and a challenge for endocrinologists, who had to implement in standard care a new drug with a unique mechanism of action which had proved highly effective in preclinical studies, but for which some uncertainties persisted regarding its long-term efficacy and safety.

Pre-marketing studies[2,3] showed the ability of PEG to dose-dependently decrease IGF-I levels, which eventually returned to normal in up to 97% of cases. However, there remained significant uncertainties: PEG caused GH hypersecretion and, in some cases, the development of specific antibodies. A potential promoting effect of tumor growth and a potential loss of efficacy were therefore feared during long-term treatment. Although the safety profile of PEG was adequate in early studies, reports of two cases of tumor growth[3] increased this fear.

Two observational, post-marketing drug surveillance studies, the German Observational Study and the ACROSTUDY (merged in the global ACROSTUDY since 2009) have provided a much greater volume of information regarding the efficacy and safety of PEG in actual clinical practice (more than 1700 patients followed up for up to 10 years)[4–7] than that available for any other treatment for acromegaly.

Normalization rates of IGF-I at five years of treatment with PEG in these studies ranged from 63 to 67% with mean doses of 17–18 mg/day in controlled patients, and somewhat higher in uncontrolled patients.[6,7] The different efficacy in pre-marketing and observational studies may be explained by the fact that the former[3] used the normalization of IGF-I at least once during treatment as a control criterion, while the latter[6,7] assessed normalization of IGF-I at a predefined time (1, 5 years, or last observation). Thus, in the Spanish ACROSTUDY cohort, the IGF-I normalization rate was higher than 67% at five years, and more than 85% of patients had normal IGF-I levels after a period of treatment

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* Corresponding author.
E-mail address: ignacio.bernabeu.moron@sergas.es (I. Bernabeu).

with mean doses of 15.2 and 17.6 mg/day respectively in controlled and uncontrolled cases (Picó A, Venegas E, Lucas T, Álvarez-Escolá C, Arnes JAG, Marazuela M, et al. Long-Term Pegvisomant Treatment Outcomes in Patients with Acromegaly: Spanish Acrostudy Data. 96th International Congress of Endocrinology/The Endocrine Society's 96th Annual Meeting. 2014: June 21–4, Chicago, Illinois). In all studies, the dose of PEG used in uncontrolled patients was lower than the maximum dose approved, which suggests the possibility of a greater efficacy with adequate dose titration. In addition, close monitoring should be performed to promote improved compliance, so avoiding factors related to treatment ineffectiveness.[8]

Some situations have been associated with greater dose requirements, including higher body weight in females, the absence of pituitary radiation therapy, higher baseline GH/IGF-I levels, diabetes,[9] or the presence of the fl/fl genotype of the GH receptor.[10] In these cases, starting doses higher than 10 mg daily might be advisable. The development of ''functional GH deficiency'' due to PEG overdosing (2.5% of cases) should be prevented,[7] so IGF-I levels should be maintained in the upper half of the normal range.

The effect of treatment with PEG on tumor volume has been comprehensively investigated,[6,11,12] and a tumor growth rate higher than that seen with other treatment modalities has not been shown. In the most recent publications from the ACROSTUDY, tumor growth rates were 3.2% in the whole series (which included 35% of combined treatments)[6] and 2.2% in patients treated with PEG monotherapy.[7] These figures are very similar to those traditionally reported for SSAs (<1–2.2%).[13] Various studies have attempted to identify factors predisposing to or promoting tumor growth during PEG treatment but with inconclusive results: patients with tumor growth showed greater increases in GH levels during the course of treatment[11] and higher GH and insulin receptor expression in the tumor.[12] By contrast, no differences have been found in angiogenesis, proliferation, or specific molecular markers.[12] Today, tumor growth during treatment with PEG can only be interpreted as resulting from the intrinsic tumor growth potential and/or the absence of an anti-proliferative effect of PEG. In this regard, the recent Endocrine Society guidelines[14] recommend the use of treatments with antitumor effect for persistent disease with large tumor remnants in contact with chiasm or vital central structures.

A small proportion of patients treated with PEG (2.5%)[6] develop reversible liver dysfunction. The incidence of liver dysfunction is greater during combined treatment with SSAs (13.5%),[15] in the presence of prior liver impairment, with the use of hepatotoxic drugs, or in diabetic patients. Mild to moderate changes usually occur. Treatment discontinuation should be considered if AST/ALT levels are more than three times the normal limit.[14] Lipohypertrophy is uncommon (2.2%),[6] usually resolves with a rotation of injection sites, and does not usually require treatment discontinuation.

PEG does not suppress insulin secretion and often improves metabolic control in diabetic patients as compared to other treatment modalities, thus making it possible to decrease hypoglycemic therapy. This positive effect on glucose metabolism is lost during combination treatment with SSAs.[9]

The combination of PEG with SSAs is used with increasing frequency, accounting for almost 50% of PEG treatments in Spain.[7] Combined treatment is indicated if severe headache occurs after SSA discontinuation or in the presence of large tumor remnants with a mass effect, in a particularly problematic location, or with prior aggressive behavior. However, these are not the most common situations in the clinical setting, which suggests that combined treatment is used in some cases to prevent a hypothetical tumor growth, or to decrease the dose or prolong the administration interval of PEG. The combination of both drugs does not achieve greater biochemical efficacy, and although it spares 0.6 mg of PEG daily (Strasburger CJ, Hey-Hadavi J, Akerblad AC, Mattsson AF, Koltowska-Haggstrom M, Wilton P, et al. Use of Combination Medical Therapy Is Common in Acromegaly. The Endocrine Society's 97th Annual Meeting. March 5–8, San Diego, California), the economic benefit is doubtful,[16] and it is associated with an increased risk of liver impairment and poorer metabolic control in diabetic patients.

To sum up, after more than 10 years of clinical use, PEG has been shown to be a safe drug with high efficacy, albeit with a slight reduction in effectiveness. The efficient use of PEG is our responsibility, and requires improvements in dose titration, follow-up, and the promotion of compliance.

Conflicts of interest

IB has received fees for lectures, advising, and research grants from Pfizer, and fees for lectures from Novartis and Ipsen. MM has received fees for lectures, advising, and research grants from Pfizer, and fees for lectures from Novartis and Ipsen.

References

1. Kopchick JJ, Parkinson C, Stevens EC, Trainer PJ. Growth hormone receptor antagonists: discovery, development, and use in patients with acromegaly. Endocr Rev. 2002;23:623–46.
2. 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. N Engl J Med. 2000;342:1171–7.
3. 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;358:1754–9.
4. Trainer PJ. ACROSTUDY: the first 5 years. Eur J Endocrinol. 2009;161 Suppl. 1:S19–24.
5. Brue T. ACROSTUDY: status update on 469 patients. Horm Res. 2009;71 Suppl. 1:S34–8.
6. Van der Lely AJ, Biller BM, Brue T, Buchfelder M, Ghigo E, Gómez R, et al. Long-term safety of pegvisomant in patients with acromegaly: Comprehensive review of 1288 subjects in ACROSTUDY. J Clin Endocrinol Metab. 2012;97:1589–97.
7. 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. Endocr Pract. 2015;21:264–74.
8. Schofl C, Grussendorf M, Honegger J, Tonjes A, Thyroke-Gronostay D, Mayr B, et al. Failure to achieve disease control in acromegaly: cause analysis by a registry-based survey. Eur J Endocrinol. 2015;172:351–6.

9. Droste M, Domberg J, Buchfelder M, Mann K, Schwanke A, Stalla G, et al. Therapy of acromegalic patients exacerbated by concomitant type 2 diabetes requires higher pegvisomant doses to normalise IGF1 levels. Eur J Endocrinol. 2014;171:59–68.
10. Bernabéu I, Álvarez-Escola C, Quinteiro C, Lucas T, Puig-Domingo M, Luque-Ramírez M, et al. The exon 3-deleted growth hormone receptor is associated with better response to pegvisomant therapy in acromegaly. J Clin Endocrinol Metab. 2010;95:222–9.
11. Buchfelder M, Weigel D, Droste M, Mann K, Saller B, Brubach K, et al. Pituitary tumor size in acromegaly during pegvisomant treatment: experience from MR re-evaluations of the German Pegvisomant Observational Study. Eur J Endocrinol. 2009;161:27–35.
12. Marazuela M, Paniagua AE, Gahete MD, Lucas T, Álvarez-Escola C, Manzanares R, et al. Somatotroph tumor progression during pegvisomant therapy: a clinical and molecular study. J Clin Endocrinol Metab. 2011;96:E251–9.
13. Besser GM, Burman P, Daly AF. Predictors and rates of treatment-resistant tumor growth in acromegaly. Eur J Endocrinol. 2005;153:187–93.
14. Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99:3933–51.
15. 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. J Clin Endocrinol Metab. 2014;99:3644–52.
16. Bernabéu I, Rodríguez-Gómez IA, Ramos-Levi AMM. Profile of pegvisomant in the management of acromegaly: an evidence based review of its place in therapy. Res Rep Endocr Disord. 2015;4:7–58.