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META-ANALYSIS

# Effectiveness and safety of pegvisomant: a systematic review and meta-analysis of observational longitudinal studies

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## Abstract

**Purpose** Acromegaly is a rare disease that often requires drug treatment to achieve control, with pegvisomant being one of the most widely used therapies. In the present paper, we aimed to obtain evidence regarding the effectiveness and safety of pegvisomant by reviewing real-world observational longitudinal studies.

**Methods** A systematic review was performed with a meta-analysis of event rates (95% confidence interval (CI)) using a random effects model. Sensitivity and subgroup analyses were performed (comprehensive meta-analysis 2.0). The systematic review was performed in accordance to preferred reporting items for systematic reviews and meta-analyses, meta-analysis of observational studies in epidemiology, and Cochrane recommendations (PROSPERO register CRD 42017059880). PubMed, Scopus, Web of Science, and SciELO were used to search for literature. Observational studies in patients using pegvisomant for the treatment of acromegaly were included.

**Results** Initially, 552 papers were retrieved from the databases; and 31 articles were included in the qualitative analysis and 14 in the quantitative analysis. Eight primary meta-analyses were performed. The overall rate of patients with disease control was of 60.9% (51.8–69.3%; 95% CI). When considering patients under monotherapy, the control rate was 71.7% (64.0–78.4%; 95% CI). Tumor growth was estimated in 7.3% (4.7–11.1%; 95% CI) and elevation of transaminases in 3.0% (1.7–5.2%; 95% CI).

**Conclusions** The real-world data showed that the effectiveness of pegvisomant is not as high as reported in interventional studies. Acromegaly appears to be better controlled when pegvisomant is used as a monotherapy. No serious adverse events were associated with the use of pegvisomant; however, given the high cost of this drug, further studies are required.

**Keywords** Acromegaly · Pituitary gland · Pegvisomant · Meta-analysis · Observational study

## Introduction

Acromegaly is a rare disease resulting from the hypersecretion of growth hormone (GH), which leads to high levels of insulin-like growth factor (IGF-1) in the circulatory system [1]. IGF-1 binds to receptors ubiquitously expressed in the human body, resulting in diverse manifestations ranging from apparent clinical features such as the enlargement of hands and feet, to more serious complications such as cardiovascular, respiratory, and metabolic comorbidities [1–3].

The main cause of acromegaly is a GH-secreting pituitary adenoma [4, 5]; and for this reason, the first therapeutic option, and the only possibility of an early cure, is tumor resection [6]. However, surgery is not always sufficient to remove the entire mass, and the disease must be controlled using other strategies such as drug therapy [6, 7].

Pegvisomant, a genetically modified analog of human GH that binds to the GH receptor and inhibits the production of IGF-1 [8], is one option for the treatment of acromegaly. In the United States, this drug is indicated for patients who had an inadequate response to surgery or radiation therapy, or for whom these therapies are not

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appropriate [9]. In Europe, adding to the aforementioned situations, pegvisomant should be used only after poor results with somatostatin analogs (SSA) [10].

Interventional studies have demonstrated a good efficacy for pegvisomant [11, 12], with a randomized controlled trial (RCT) and study extension showing levels of IGF-1 control as high as 89% and 97%, respectively [13, 14]. However, since pegvisomant does not act directly in the tumor, patients undertaking this therapy should be monitored for tumor growth by magnetic resonance imaging (MRI). The elevation of liver enzymes has also been reported as an important adverse event (AE) [2]. Yet, the literature lacks further analysis of the long-term effectiveness and safety of pegvisomant in patients with acromegaly.

Observational studies are increasingly used to assess the real-world effectiveness and safety of drugs outside the highly controlled environment of clinical trials. Moreover, real-world studies typically encompass a much larger population than RCTs, which is particularly important when dealing with rare diseases [15]. In a real word scenario, clinicians may choose the best treatment option for each patient depending on their characteristics and preferences, which contributes to a better adherence to the therapy and leads to improvement in clinical results [16]. Therefore, we aimed to perform a systematic review with meta-analysis of longitudinal observational studies to evaluate the effectiveness and safety of pegvisomant in the treatment of acromegaly in real settings.

## Methods

### Eligibility criteria for systematic review

A systematic review was conducted following preferred reporting items for systematic reviews and meta-analyses, meta-analysis of observational studies in epidemiology, and Cochrane Collaboration recommendations [17–19]. All steps were independently performed by two authors, with a third author consulted when disagreements appeared.

A systematic search was conducted in PubMed, Web of Science, Scopus, and SciELO in March 2018. A manual search in the reference lists of included studies was also performed. If a record was not found online, we contacted the authors by e-mail. The following descriptors were used to build the search strategies: *acromegaly*, *pegvisomant*, *observational study*, and *longitudinal study*, among others, which were combined with the Boolean operators *AND* and *OR*. The full search strategy can be viewed in the Supplementary material.

Studies were included if they met the following eligibility criteria: (1) patients diagnosed with acromegaly; (2) patients using pegvisomant in monotherapy or in association; (3) observational longitudinal studies with or without a comparator group; and (4) studies reporting effectiveness outcomes of IGF-1 control or safety outcomes (AEs). Studies that did not address outcomes of interest, other types of studies (e.g., interventional studies), those that evaluated other drugs used for acromegaly, and papers published in non-Roman characters were excluded.

### Data extraction and quality assessment

The data extracted from the records consisted of the following: (1) paper meta-data (authors' names, year of publication, country(ies) of study conduction, period of study, and study design); (2) baseline characteristics (number of patients, gender, age, age at diagnosis, comorbidities, previous treatments for acromegaly, and pegvisomant treatment data); (3) effectiveness data (number of patients with IGF-1 control); and (4) safety data (number of patients with tumor growth following the initiation of pegvisomant therapy as assessed by local and central MRI, number of patients with other AEs, and number of patients who discontinued therapy due to AEs. MRI was classified as *local* when interpreted by a local neuroradiologist or radiologist, and *central* when sent to another center to be assessed by a radiologist blinded to all clinical data).

The methodological quality of the studies was assessed by the Newcastle–Ottawa Scale (NOS) [20].

### Statistical analysis

Meta-analyses of event rates were performed using the random effects model with logit transformation. The random model was chosen in order to consider a possible heterogeneity among studies. The rates are presented with lower and upper limits of 95% confidence interval (CI). Heterogeneity was assessed using Chi-square and $I^2$ statistical tests, and was considered substantial at $p < 0.05$ and high at $I^2 > 75\%$ [17]. Sensitivity analyses with changes in the statistical models and methods were performed to explore heterogeneity. We hypothetically removed studies from the meta-analysis to assess the impact of any individual study on heterogeneity. Where possible, subgroup analyses were performed. All analyses were conducted using comprehensive meta-analysis version 2.

## Results

The database search retrieved 346 records following the removal of duplicates. A total of 68 papers were included in

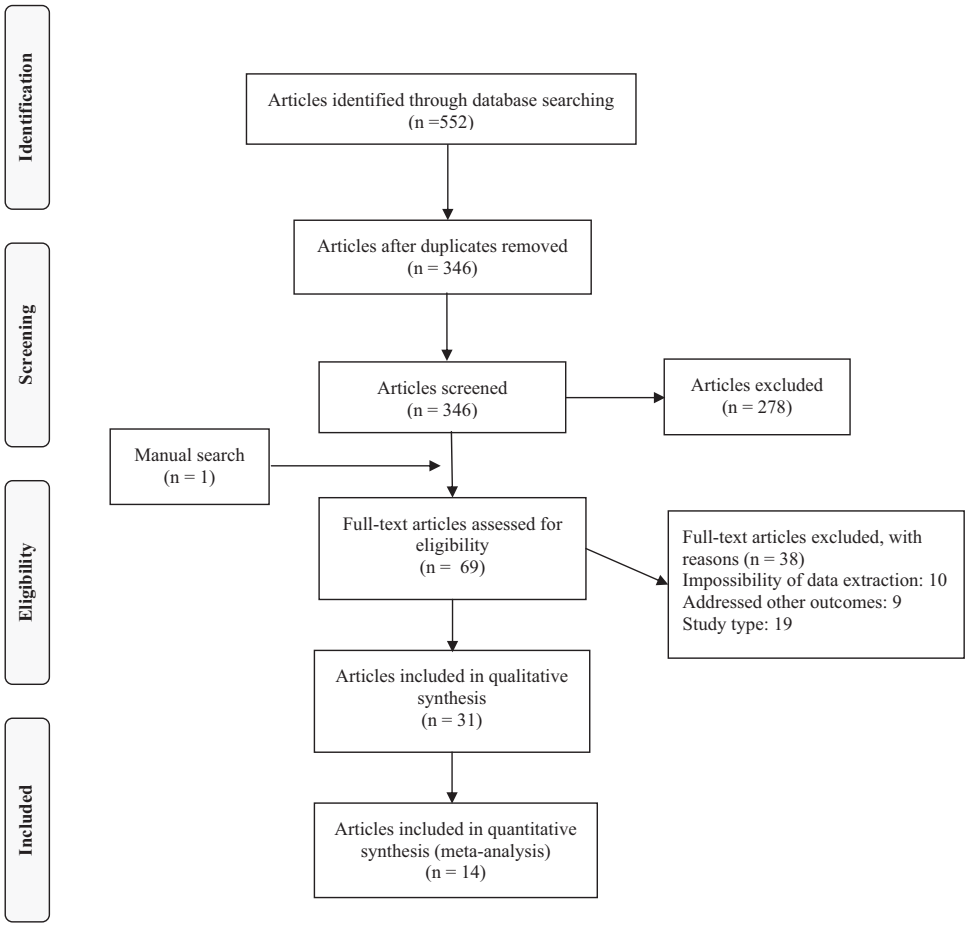


**Fig. 1** PRISMA flowchart of study selection

the full-text reading phase, and one paper was added following a manual search. Finally, 31 articles [21–51] met all eligibility criteria and were included in the systematic review. To avoid patient duplication, only one study from each country was included in the meta-analyses, i.e., the most recent or the one with the most complete information for each outcome; therefore, 14 studies [27, 29–31, 33, 34, 39, 42, 46–51] were evaluated in the quantitative analyses (Fig. 1).

## Study characteristics

Most of the 31 articles included in the systematic review reported patients who were part of ACROSTUDY, an observational registry intended to collect safety and efficacy data on pegvisomant therapy. Six papers presented data of patients from all the countries involved in ACROSTUDY, which varied from 10 to 14 depending on the time of analysis, namely: Germany, France, Italy, Spain, the Netherlands, the United States, the United Kingdom, Greece, Denmark, Belgium, Sweden, Slovakia, Portugal, and Hungary. The other 15 articles included in the systematic review presented results of patients from only one country each: Germany, Italy, Spain, France, Denmark, Greece, Turkey, Argentina, and Brazil. Only the latter three countries were not part of ACROSTUDY.

The meta-data and patient baseline characteristics from all studies are shown in Table S1 (Supplementary material). The most frequent comorbidity was diabetes, with a prevalence of approximately 30% in almost all studies. The age of the patients at diagnosis was approximately 40 years old. The previous patient treatments included surgery, radiotherapy, and drug therapy (dopamine agonist, represented by cabergoline, and the somatostatin analogs, octreotide, and lanreotide). Treatment duration ranged from 1 year [21] to $5.4 \pm 2.6$ years [46] and patients undergoing monotherapy varied from 0% [36, 43] to 100% [24, 25, 31, 39, 47]. Dose and frequencies were variable between studies and patients.

Overall, the papers showed similar methodological quality, with no major deficiencies in the description of patient inclusion criteria or data collection. The follow-up period in all studies was greater than 6 months, which is considered sufficient to observe the effects of pegvisomant. Few patient withdrawals were reported (Supplementary material).

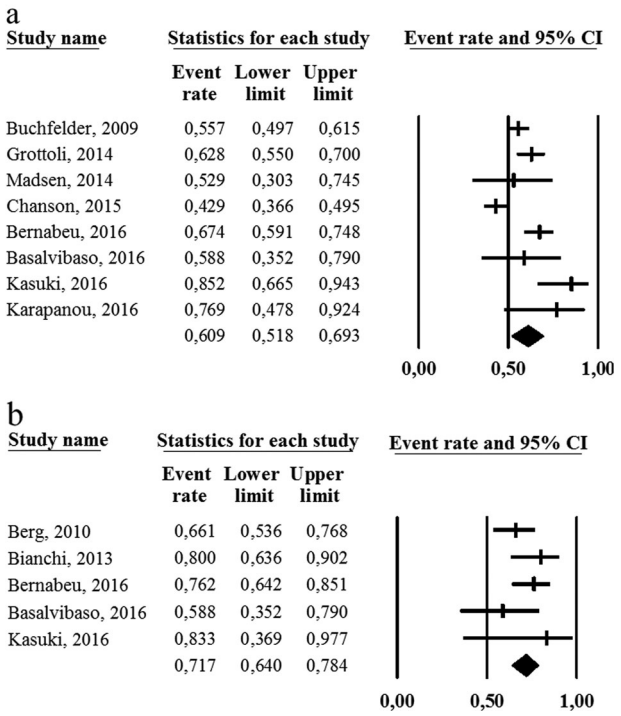


**Fig. 2** Meta-analysis results for the rate of patients achieving IGF-1 control under pegvisomant therapy (**a**) and under pegvisomant monotherapy (**b**). *Note*: fixed effects model, event rate with 95% confidence interval

## Meta-analysis

Eight meta-analyses were performed; two generating results from effectiveness outcomes (IGF-1 control) and six considering data on safety outcomes (tumor growth, injection-site reactions, lipohypertrophy, elevation of transaminases, and treatment discontinuation due to AE). It was not possible to conduct analysis considering only patients under combination therapy, because studies reported results either for all cohort of patients (irrespective of drug association or not) or solely for patients under monotherapy.

The meta-analysis of patients achieving IGF-1 control included eight studies and resulted in an overall rate of 60.9% (51.8–69.3%; 95% CI; $I^2 = 80\%$; Fig. 2a). The meta-analysis considering only patients undergoing pegvisomant monotherapy ($n = 5$ studies) resulted in an overall IGF-1 control rate of 71.7% (64.0–78.4%; 95% CI; $I^2 = 10\%$; Fig. 2b).

Regarding safety outcomes, five meta-analyses were performed. For the outcome of tumor growth, an additional meta-analysis considering only patients under pegvisomant monotherapy was feasible. The overall tumor growth rate in patients undergoing pegvisomant therapy in association with another drug or alone (local MRI, eight studies) was 7.3% (4.7–11.1%; 95% CI; $I^2 = 58\%$). When considering only patients who received monotherapy ($n = 4$ studies), the rates were 7.2% (4.8–10.7%; 95% CI; $I^2 = 0\%$). Statistical analyses for central MRI were not possible. The meta-analysis of elevated transaminases ($n = 6$ studies) showed an overall rate of 3.0% (1.7–5.2%; 95% CI; $I^2 = 55\%$). The outcomes of injection-site reaction ($n = 4$ studies) and lipohypertrophy ($n = 5$ studies) presented values of 3.5% (1.2–10.2%; 95% CI; $I^2 = 82\%$) and 1.6% (0.6–4.3%; 95% CI; $I^2 = 69\%$), respectively. The rate of patients who discontinued pegvisomant due to an AE that was deemed related to the therapy was 1.9% (0.6–5.9%; 95% CI; $I^2 = 78\%$). The forest plots for these meta-analyses are depicted in Fig. 3.

## Sensitivity and subgroup analyses

Sensitivity analyses were performed with 8 meta-analyses, presenting moderate ($I^2$ between 50% and 75%) to high heterogeneity ($I^2 > 75\%$). Removal of studies and changes to the statistical model and methods revealed no significant differences as compared with the original meta-analyses.

Subgroup analyses were performed to evaluate the impact of study follow-up duration on IGF-1 control. Studies reporting data over 1–5 years were evaluated in separate meta-analyses. The event rates ranged from 57% to 65% (for complete meta-analyses see Supplementary material).

# Discussion

To the best of our knowledge, this is the first meta-analysis of longitudinal observational studies on the use of pegvisomant in acromegaly, which is a milestone with respect to rare diseases. This was only possible due to the increased number of publications on the subject in the last few years, which allowed us to gather evidence from several countries.

The most recognized study in the field (ACROSTUDY) is a postmarketing surveillance study sponsored by Pfizer, which was initiated in 2004 and includes 15 countries from Europe and the United States; however, other locations such as Brazil and Argentina have also conducted observational studies.

Pegvisomant is a genetically engineered analog of human GH that has been available on the market since 2004 [52–54], and is considered the most effective pharmaceutical therapy for acromegaly in clinical trials. However, real-world data indicate that its effectiveness is not as high as expected [53]. We found rates of patient achievement of IGF-1 control of approximately 61% when used in conjunction with other drugs and 72% when used as a monotherapy, which is at least 25% below the rates reported in interventional studies [13, 14]. The results of the analyses of IGF-1 control at different time points were similar (event

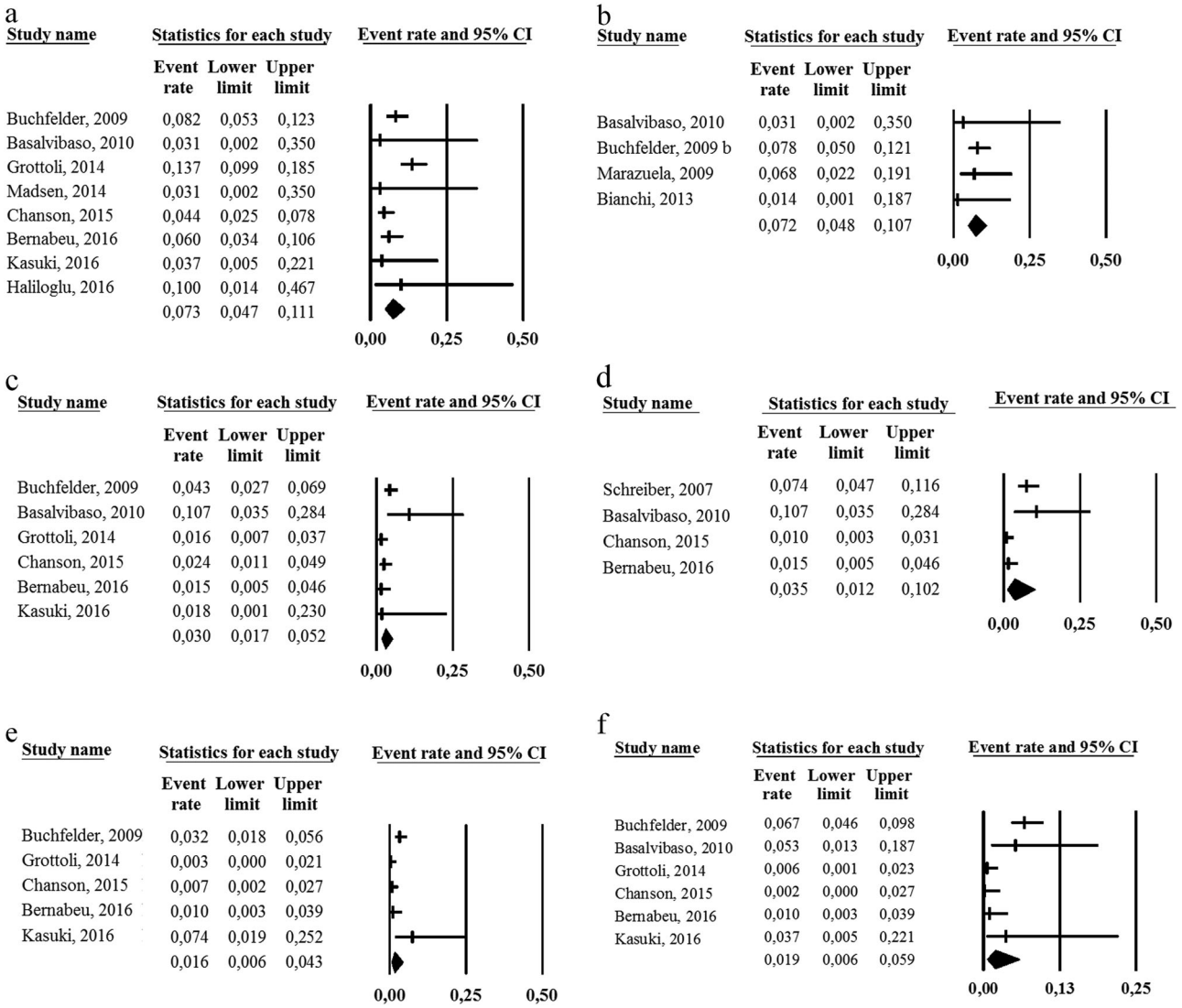


**Fig. 3** Meta-analysis results for safety outcomes. Tumor growth verified by local magnetic resonance imaging (**a**); elevation of transaminases (**b**); injection-site reactions (**c**); lipohypertrophy (**d**); and discontinuation due to adverse events (**e**). *Note*: fixed effects model, event rate with 95% confidence interval

rates fluctuating around 60%), showing that the actual effect of pegvisomant, although lower than in controlled trials, may be homogeneous over time, which is important given the chronicity of the disease.

The highest rates of IGF-1 control were observed when pegvisomant was used as a monotherapy [52], which is in accordance with data reported in interventional studies. Hypotheses to explain this result can be the use of higher doses of the drug when under monotherapy, or the characteristic of patients that receive combination therapy. The article from Bianchi et al. [33] showed that the choice of associating SSA to pegvisomant is significantly related to the presence of residual tumor at baseline and to patients with higher rates of GH and IGF-1 at baseline, i.e., a more aggressive disease. The start of pegvisomant only after SSA unsuccessful treatment may also explain the lower rates of effectiveness observed in real-life when compared to clinical trials where pegvisomant was, in many cases, the first drug received by patients [13, 55].

Combination therapy is not described on the pegvisomant label; however, this drug is frequently used in conjunction with a somatostatin analog in clinical practice [53]. This is endorsed by the potential increase in the efficacy of pegvisomant when used in association with a somatostatin analog [8]. However, our results do not confirm this effect. Another advantage of the co-therapy may be the reduction in the incidence of AE, such as tumor growth. Since somatostatin analogs act directly in the tumor, unlike pegvisomant, they do not cause tumor augmentation, and can even contribute to a reduction in the tumor size [56, 57].

Drug combination is also a way to minimize therapy costs, if pegvisomant is prescribed at lower doses, due to the high costs of this drug (approximately 100 USD per 10 mg vial, drugbank.ca/drugs/DB00082, access date: 05/14/2018).

The monitoring of AEs is one of the main objectives of long-term observational studies. In the literature, one of the most reported AEs for pegvisomant is an increase in the levels of liver enzymes [2]. In the present study, we found this rate to be 3%; however, certain papers included in this review reported that the elevation of liver enzymes returned to normal with continuous use of the drug [22, 27–29, 49], which suggests that the rate of this AE may have been overestimated; nevertheless, liver function should be constantly monitored. Regarding tumor growth, we found an event rate of 7% for both analysis, including all patients using pegvisomant and only those under monotherapy. It is known that SSAs, which act directly on the somatotropinoma, may contribute to reduce tumor size. However, the rates found in our study were very similar for both populations assessed. This finding does not mean that SSA combination therapy do not contribute to tumor reduction but may suggest that pegvisomant alone do not favor tumor enlargement. When a blinded radiologist performed the analysis of tumor growth, the prevalence was lower than that seen in the local MRI findings [23–27, 30, 34, 35, 40]. However, since few studies reporting data on central MRI were found, no meta-analysis was performed. Injection-site reactions, mainly represented by lipohypertrophy, were associated with the pharmaceutical formulation and administration route of pegvisomant (subcutaneous injections). In the present study, we found rates of 3% and 2% for these two outcomes, respectively. These events can be prevented by diversity of injection site [8, 41]. The rate of discontinuation due to AEs related to study treatment was estimated to be 2%; nevertheless, this is a subjective outcome, since it depends on the opinion of the clinician whether the AE is actually associated with the drug. We observed a study with many more discontinuations than the others [29]; however, the authors stated that the discontinuations were potentially related to the therapy but gave no certainty. The AEs that led to treatment discontinuation were mainly the elevation of transaminases and apparent tumor enlargement. Overall, therapy with pegvisomant appears to be safe.

The present study has some limitations. Unfortunately, we could not include all the studies obtained in our systematic review in the meta-analyses, since patients were reported more than once. We confirmed the authors' names and affiliations for all the studies (i.e., countries and hospitals listed as institutions) to avoid misleading results. We evaluated only observational studies, which can have been an influenced by confounders; nevertheless, these studies have a more appropriate design to describe the prevalence of events and assess real-world evidence. We were not able to conduct separate analysis for patients who received only combination therapy, because the studies did not disclose this information. Therefore, meta-analyses were performed for patients receiving pegvisomant in association or not, and for patients receiving pegvisomant in monotherapy. Heterogeneity among studies was explored wherever possible; however, according to the Cochrane recommendations, it is not appropriate to deeply evaluate heterogeneity when only a few articles are included in the meta-analyses, since erroneous conclusions may be generated [17]. To calculate the effect sizes in the meta-analyses, we used a logit transformation. When the number of events is zero and the population is small, this transformation may result in inflation of the results [58]. The absence of events was observed for three outcomes; elevation of transaminases, tumor growth, and discontinuation due to AEs. Therefore, the rates of these outcomes are likely even smaller. Taking all the data together, we can affirm that we performed a conservative analysis and that the actual effectiveness and safety results should not be expected to be any higher than our estimations.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. K. Gunawardane, T. Krarup Hansen, J. Sandahl Christiansen, J.O. Lunde Jorgensen, Normal physiology of growth hormone in adults. in L.J. De Groot, G. Chrousos, K. Dungan, K.R. Feingold, A. Grossman, J.M. Hershman, C. Koch, M. Korbonits, R. McLachlan, M. New, J. Purnell, R. Rebar, F. Singer, A. Vinik (eds.) Endotext. (South Dartmouth, MA, 2000)
2. L. Katznelson, E.R. Laws Jr., S. Melmed, M.E. Molitch, M.H. Murad, A. Utz, J.A. Wass, S. Endocrine, Acromegaly: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. **99**(11), 3933–3951 (2014). https://doi.org/10.1210/jc.2014-2700
3. A. Colao, D. Ferone, P. Marzullo, G. Lombardi, Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr. Rev. **25**(1), 102–152 (2004). https://doi.org/10.1210/er.2002-0022
4. S. Melmed, Acromegaly pathogenesis and treatment. J. Clin. Invest **119**(11), 3189–3202 (2009). https://doi.org/10.1172/JCI39375
5. P. Chanson, S. Salenave, P. Kamenicky, Acromegaly. Handb. Clin. Neurol. **124**, 197–219 (2014). https://doi.org/10.1016/B978-0-444-59602-4.00014-9

6. S. Stormann, J. Schopohl, Perspectives on investigational drugs for acromegaly. Expert Opin. Investig. Drugs **25**(4), 381–384 (2016). https://doi.org/10.1517/13543784.2016.1142530
7. J.M. Silverstein, Need for improved monitoring in patients with acromegaly. Endocr. Connect **4**(4), R59–67 (2015). https://doi.org/10.1530/EC-15-0064
8. S.J. Neggers, A. Muhammad, A.J. van der Lely, Pegvisomant treatment in acromegaly. Neuroendocrinology **103**(1), 59–65 (2016). https://doi.org/10.1159/000381644
9. FDA: Pegvisomant Approval (2018), https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed 19 July 2018
10. EMA: Pegvisomant Approval (2018).
11. D.J. Moore, Y. Adi, M.J. Connock, S. Bayliss, Clinical effectiveness and cost-effectiveness of pegvisomant for the treatment of acromegaly: a systematic review and economic evaluation. BMC Endocr. Disord. **9**, 20 (2009). https://doi.org/10.1186/1472-6823-9-20
12. L.P. Leonart, V.L. Ferreira, F.S. Tonin, F. Fernandez-Llimos, R. Pontarolo, Medical treatments for acromegaly: a systematic review and network meta-analysis. Value Health **21**(7), 874–880 (2018). https://doi.org/10.1016/j.jval.2017.12.014
13. P.J. Trainer, W.M. Drake, L. Katznelson, P.U. Freda, V. Herman-Bonert, A.J. van der Lely, E.V. Dimaraki, P.M. Stewart, K.E. Friend, M.L. Vance, G.M. Besser, J.A. Scarlett, M.O. Thorner, C. Parkinson, A. Klibanski, J.S. Powell, A.L. Barkan, M.C. Sheppard, M. Malsonado, D.R. Rose, D.R. Clemmons, G. Johannsson, B.A. Bengtsson, S. Stavrou, D.L. Kleinberg, D.M. Cook, L.S. Phillips, M. Bidlingmaier, C.J. Strasburger, S. Hackett, K. Zib, W.F. Bennett, R.J. Davis, Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N. Engl. J. Med **342**(16), 1171–1177 (2000). https://doi.org/10.1056/NEJM200004203421604
14. A.J. van der Lely, R.K. Hutson, P.J. Trainer, G.M. Besser, A.L. Barkan, L. Katznelson, A. Klibanski, V. Herman-Bonert, S. Melmed, M.L. Vance, P.U. Freda, P.M. Stewart, K.E. Friend, D. R. Clemmons, G. Johannsson, S. Stavrou, D.M. Cook, L.S. Phillips, C.J. Strasburger, S. Hackett, K.A. Zib, R.J. Davis, J.A. Scarlett, M.O. Thorner, Long-term treatment of acromegaly with pegvisomant, a growth hormone-receptor antagonist. Lancet **358** (9295), 1754–1759 (2001)
15. S. de Lusignan, L. Crawford, N. Munro, Creating and using real-world evidence to answer questions about clinical effectiveness. J. Innov. Health Inform. **22**(3), 368–373 (2015). https://doi.org/10.14236/jhi.v22i3.177
16. M.L. Berger, H. Sox, R.J. Willke, D.L. Brixner, H.G. Eichler, W. Goettsch, D. Madigan, A. Makady, S. Schneeweiss, R. Tarricone, S.V. Wang, J. Watkins, C. Daniel Mullins, Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in healthcare decision making. Pharmacoepidemiol. Drug Saf. **26**(9), 1033–1039 (2017). https://doi.org/10.1002/pds.4297
17. J.P.T. Higgins, G.S.: Cochrane handbook for systematic reviews of interventions, version 5.1.0. The Cochrane Collaboration (2011).
18. A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gotzsche, J.P. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Br Med J **339**, b2700 (2009). https://doi.org/10.1136/bmj.b2700
19. D.F. Stroup, J.A. Berlin, S.C. Morton, I. Olkin, G.D. Williamson, D. Rennie, D. Moher, B.J. Becker, T.A. Sipe, S.B. Thacker, Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. J Am Med Assoc **283**(15), 2008–2012 (2000)
20. G.A. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed 13 June 2018
21. T. Brue, ACROSTUDY: status update on 469 patients. Horm. Res. **71**(Suppl 1), S34–S38 (2009). https://doi.org/10.1159/000178035
22. P.J. Trainer, ACROSTUDY: the first 5 years. Eur. J. Endocrinol. **161**(Suppl 1), S19–S24 (2009). https://doi.org/10.1530/EJE-09-0322
23. A.J. van der Lely, B.M. Biller, T. Brue, M. Buchfelder, E. Ghigo, R. Gomez, J. Hey-Hadavi, F. Lundgren, N. Rajicic, C.J. Strasburger, S.M. Webb, M. Koltowska-Haggstrom, Long-term safety of pegvisomant in patients with acromegaly: comprehensive review of 1288 subjects in ACROSTUDY. J. Clin. Endocrinol. Metab. **97**(5), 1589–1597 (2012). https://doi.org/10.1210/jc.2011-2508
24. P.U. Freda, M.B. Gordon, N. Kelepouris, P. Jonsson, M. Koltowska-Haggstrom, A.J. van der Lely, Long-term treatment with pegvisomant as monotherapy in patients with acromegaly: experience from ACROSTUDY. Endocr. Pract. **21**(3), 264–274 (2015). https://doi.org/10.4158/EP14330.OR
25. N.A. Tritos, P. Chanson, C. Jimenez, D. King, P.J. Jonsson, A. Klibanski, B.M. Biller, Effectiveness of first-line pegvisomant monotherapy in acromegaly: an ACROSTUDY analysis. Eur. J. Endocrinol. **176**(2), 213–220 (2017). https://doi.org/10.1530/EJE-16-0697
26. C.J. Strasburger, A. Mattsson, P. Wilton, F. Aydin, J. Hey-Hadavi, B.M.K. Biller, Increasing frequency of combination medical therapy in the treatment of acromegaly with the GH receptor antagonist pegvisomant. Eur. J. Endocrinol. **178**(4), 321–329 (2018). https://doi.org/10.1530/EJE-17-0996
27. I. Schreiber, M. Buchfelder, M. Droste, K. Forssmann, K. Mann, B. Saller, C.J. Strasburger, I. German Pegvisomant, Treatment of acromegaly with the GH receptor antagonist pegvisomant in clinical practice: safety and efficacy evaluation from the German Pegvisomant Observational Study. Eur. J. Endocrinol. **156**(1), 75–82 (2007). https://doi.org/10.1530/eje.1.02312
28. C.J. Strasburger, M. Buchfelder, M. Droste, K. Mann, G.K. Stalla, B. Saller, I. German Pegvisomant, Experience from the German pegvisomant observational study. Horm. Res. **68**(Suppl 5), S70–S73 (2007). https://doi.org/10.1159/000110481
29. M. Buchfelder, S. Schlaffer, M. Droste, K. Mann, B. Saller, K. Brubach, G.K. Stalla, C.J. Strasburger; German Pegvisomant Observational Study, The German ACROSTUDY: past and present. Eur. J. Endocrinol. **161**(Suppl 1), S3–S10 (2009). https://doi.org/10.1530/EJE-09-0350
30. M. Buchfelder, D. Weigel, M. Droste, K. Mann, B. Saller, K. Brubach, G.K. Stalla, M. Bidlingmaier, C.J. Strasburger, Investigators of German Pegvisomant Observational Study. Pituitary tumor size in acromegaly during pegvisomant treatment: experience from MR re-evaluations of the German Pegvisomant Observational Study. Eur. J. Endocrinol. **161**(1), 27–35 (2009). https://doi.org/10.1530/EJE-08-0910
31. C. Berg, S. Petersenn, H. Lahner, B.L. Herrmann, M. Buchfelder, M. Droste, G.K. Stalla, C.J. Strasburger, U. Roggenbuck, N. Lehmann, S. Moebus, K.H. Jockel, S. Mohlenkamp, R. Erbel, B. Saller, K. Mann; Investigative Group of the Heinz Nixdorf Recall Study and the German Pegvisomant Observational Study Board and Investigators, Cardiovascular risk factors in patients with uncontrolled and long-term acromegaly: comparison with matched data from the general population and the effect of disease control. J. Clin. Endocrinol. Metab. **95**(8), 3648–3656 (2010). https://doi.org/10.1210/jc.2009-2570
32. C. Urbani, C. Sardella, A. Calevro, G. Rossi, I. Scattina, M. Lombardi, I. Lupi, L. Manetti, E. Martino, F. Bogazzi, Effects of

medical therapies for acromegaly on glucose metabolism. Eur. J. Endocrinol. **169**(1), 99–108 (2013). https://doi.org/10.1530/EJE-13-0032
33. A. Bianchi, F. Valentini, R. Iuorio, M. Poggi, R. Baldelli, M. Passeri, A. Giampietro, L. Tartaglione, S. Chiloiro, M. Appetecchia, P. Gargiulo, A. Fabbri, V. Toscano, A. Pontecorvi, L. De Marinis, Long-term treatment of somatostatin analog-refractory growth hormone-secreting pituitary tumors with pegvisomant alone or combined with long-acting somatostatin analogs: a retrospective analysis of clinical practice and outcomes. J. Exp. Clin. Cancer Res **32**, 40 (2013). https://doi.org/10.1186/1756-9966-32-40
34. S. Grottoli, P. Maffei, F. Bogazzi, S. Cannavo, A. Colao, E. Ghigo, R. Gomez, E. Graziano, M. Monterubbianesi, P. Jonsson, L. De Marinis, ACROSTUDY: the Italian experience. Endocrine **48**(1), 334–341 (2015). https://doi.org/10.1007/s12020-014-0393-9
35. S. Cannavo, F. Bogazzi, A. Colao, L. De Marinis, P. Maffei, R. Gomez, E. Graziano, M. Monterubbianesi, S. Grottoli, G. Italian Acrostudy, Does pegvisomant treatment expertise improve control of resistant acromegaly? The Italian ACROSTUDY experience. J. Endocrinol. Invest **38**(10), 1099–1109 (2015). https://doi.org/10.1007/s40618-015-0289-4
36. R.S. Auriemma, L.F. Grasso, M. Galdiero, M. Galderisi, C. Pivonello, C. Simeoli, M.C. De Martino, R. Ferrigno, M. Negri, C. de Angelis, R. Pivonello, A. Colao, Effects of long-term combined treatment with somatostatin analogues and pegvisomant on cardiac structure and performance in acromegaly. Endocrine **55**(3), 872–884 (2017). https://doi.org/10.1007/s12020-016-0995-5
37. M. Ragonese, S. Grottoli, P. Maffei, A. Alibrandi, M.R. Ambrosio, G. Arnaldi, A. Bianchi, S. Puglisi, M.C. Zatelli, L. De Marinis, E. Ghigo, A. Giustina, F. Maffezzoni, C. Martini, L. Trementino, S. Cannavo, How to improve effectiveness of pegvisomant treatment in acromegalic patients. J. Endocrinol. Invest. (2017). https://doi.org/10.1007/s40618-017-0773-0
38. S. Chiloiro, G. Mazziotti, A. Giampietro, A. Bianchi, S. Frara, M. Mormando, A. Pontecorvi, A. Giustina, L. De Marinis, Effects of pegvisomant and somatostatin receptor ligands on incidence of vertebral fractures in patients with acromegaly. Pituitary (2018). https://doi.org/10.1007/s11102-018-0873-7
39. M. Marazuela, T. Lucas, C. Alvarez-Escola, M. Puig-Domingo, N.G. de la Torre, P. de Miguel-Novoa, A. Duran-Hervada, R. Manzanares, M. Luque-Ramirez, I. Halperin, F.F. Casanueva, I. Bernabeu, Long-term treatment of acromegalic patients resistant to somatostatin analogues with the GH receptor antagonist pegvisomant: its efficacy in relation to gender and previous radiotherapy. Eur. J. Endocrinol. **160**(4), 535–542 (2009). https://doi.org/10.1530/EJE-08-0705
40. M. Marazuela, A.E. Paniagua, M.D. Gahete, T. Lucas, C. Alvarez-Escola, R. Manzanares, J. Cameselle-Teijeiro, M. Luque-Ramirez, R.M. Luque, E. Fernandez-Rodriguez, J.P. Castano, I. Bernabeu, Somatotroph tumor progression during pegvisomant therapy: a clinical and molecular study. J. Clin. Endocrinol. Metab. **96**(2), E251–259 (2011). https://doi.org/10.1210/jc.2010-1742
41. G. Sesmilo, E. Resmini, I. Bernabeu, J. Aller, A. Soto, M. Mora, A. Pico, C. Fajardo, E. Torres, C. Alvarez-Escola, R. Garcia, C. Blanco, R. Camara, S. Gaztambide, I. Salinas, C.D. Pozo, I. Castells, C. Villabona, B. Biagetti, S.M. Webb, Escape and lipodystrophy in acromegaly during pegvisomant therapy, a retrospective multicentre Spanish study. Clin. Endocrinol. **81**(6), 883–890 (2014). https://doi.org/10.1111/cen.12440
42. I. Bernabeu, A. Pico, E. Venegas, J. Aller, C. Alvarez-Escola, J.A. Garcia-Arnes, M. Marazuela, P. Jonsson, N. Mir, M. Garcia Vargas, A.G. Spanish, Safety of long-term treatment with Pegvisomant: analysis of Spanish patients included in global ACROSTUDY. Pituitary **19**(2), 127–137 (2016). https://doi.org/10.1007/s11102-015-0691-0
43. M. Puig-Domingo, A. Soto, E. Venegas, R. Vilchez, C. Blanco, F. Cordido, T. Lucas, M. Marazuela, R. Casany, G. Cuatrecasas, C. Fajardo, M.A. Galvez, S. Maraver, T. Martin, E. Romero, M. Paja, A. Pico, I. Bernabeu, E. Resmini; ACROCOMB study group, Use of lanreotide in combination with cabergoline or pegvisomant in patients with acromegaly in the clinical practice: the ACROCOMB study. Endocrinol. Nutr. **63**(8), 397–408 (2016). https://doi.org/10.1016/j.endonu.2016.05.010
44. A.M. Ramos-Levi, I. Bernabeu, C. Alvarez-Escola, J. Aller, T. Lucas, P. de Miguel, L. Rodriguez-Canete, M.A. Sampedro-Nunez, I. Halperin, M. Puig-Domingo, M. Marazuela, Long-term treatment with pegvisomant for acromegaly: a 10-year experience. Clin. Endocrinol. **84**(4), 540–550 (2016). https://doi.org/10.1111/cen.12993
45. E. Kuhn, L. Maione, A. Bouchachi, M. Roziere, S. Salenave, S. Brailly-Tabard, J. Young, P. Kamenicky, P. Assayag, P. Chanson, Long-term effects of pegvisomant on comorbidities in patients with acromegaly: a retrospective single-center study. Eur. J. Endocrinol. **173**(5), 693–702 (2015). https://doi.org/10.1530/EJE-15-0500
46. P. Chanson, T. Brue, B. Delemer, P. Caron, F. Borson-Chazot, H. Zouater, Medecins de l'Etude ACROSTUDY. Pegvisomant treatment in patients with acromegaly in clinical practice: the French ACROSTUDY. Ann. Endocrinol. **76**(6), 664–670 (2015). https://doi.org/10.1016/j.ando.2015.10.003
47. N.G. Basavilbaso, M. Guitelman, A. Nagelberg, G. Stalldecker, A. Carabelli, O. Bruno, K. Danilowitz, M. Manavela, S. Mallea Gil, C. Ballarino, R. Guelman, D. Katz, S. Fidalgo, R. Leal, H. Fideleff, M. Servidio, D. Bruera, F. Librandi, A. Chervin, M. Vitale, A. Basso, Experience from the Argentine Pegvisomant Observational Study: preliminary data. Front. Horm. Res. **38**, 42–49 (2010). https://doi.org/10.1159/000318493
48. M. Madsen, S. Fisker, U. Feldt-Rasmussen, M. Andreassen, L.O. Kristensen, H. Orskov, J.O. Jorgensen, Circulating levels of pegvisomant and endogenous growth hormone during prolonged pegvisomant therapy in patients with acromegaly. Clin. Endocrinol. **80**(1), 92–100 (2014). https://doi.org/10.1111/cen.12239
49. L. Kasuki, E.O. Machado, L.L. Ogino, M.C. Coelho, C.M. Silva, L.E. Wildemberg, C.H. Lima, M.R. Gadelha, Experience with pegvisomant treatment in acromegaly in a single Brazilian tertiary reference center: efficacy, safety and predictors of response. Arch. Endocrinol. Metab. **60**(5), 479–485 (2016). https://doi.org/10.1590/2359-3997000000210
50. O. Haliloglu, E. Kuruoglu, H.M. Ozkaya, F.E. Keskin, O. Gunaldi, B. Oz, N. Gazioglu, P. Kadioglu, N. Tanriover, Multidisciplinary approach for acromegaly: a single tertiary center's experience. World Neurosurg. **88**, 270–276 (2016). https://doi.org/10.1016/j.wneu.2015.12.092
51. O. Karapanou, M. Tzanela, M. Christoforaki, L. Papastathopoulou, P. Moutsatsou, E. Botoula, S. Tsagarakis, Therapeutic trends and outcome of acromegaly: a single-center experience over a 40-year period. Hormones **15**(3), 368–376 (2016). https://doi.org/10.14310/horm.2002.1680
52. L. Ferreri, R.S. Auriemma, L.F.S. Grasso, R. Pivonello, A. Colao , Efficacy and tolerability of treatment with pegvisomant in acromegaly: an overview of literature. Expert Opinion on Orphan. Drugs **3**(1), 12 (2015). https://doi.org/10.1517/21678707.2014.970171
53. A. Giustina, G. Arnaldi, F. Bogazzi, S. Cannavo, A. Colao, L. De Marinis, E. De Menis, E. Degli Uberti, F. Giorgino, S. Grottoli, A. G. Lania, P. Maffei, R. Pivonello, E. Ghigo, Pegvisomant in acromegaly: an update. J. Endocrinol. Invest. **40**(6), 577–589 (2017). https://doi.org/10.1007/s40618-017-0614-1

54. A.N. Paisley, P. Trainer, W. Drake, Pegvisomant: a novel pharmacotherapy for the treatment of acromegaly. Expert Opin. Biol. Ther. **4**(3), 421–425 (2004). https://doi.org/10.1517/14712598.4.3.421
55. E. Ghigo, B.M. Biller, A. Colao, I.A. Kourides, N. Rajicic, R.K. Hutson, L. De Marinis, A. Klibanski, Comparison of pegvisomant and long-acting octreotide in patients with acromegaly naive to radiation and medical therapy. J. Endocrinol. Invest. **32**(11), 924–933 (2009). https://doi.org/10.3275/672310.1007/BF03345774
56. A. Colao, R.S. Auriemma, R. Pivonello, The effects of somatostatin analogue therapy on pituitary tumor volume in patients with acromegaly. Pituitary **19**(2), 210–221 (2016). https://doi.org/10.1007/s11102-015-0677-y
57. G. Mazziotti, A. Giustina, Effects of lanreotide SR and autogel on tumor mass in patients with acromegaly: a systematic review. Pituitary **13**(1), 60–67 (2010). https://doi.org/10.1007/s11102-009-0169-z
58. M.J. Rousseau, J.C. Evans, Key statistical assumptions and methods in one arm meta-analyses with binary endpoints and low event rates, including a real-life example in the area of endoscopic colonic stenting. Cogent Med **4**(1), 1334318 (2017). https://doi.org/10.1080/2331205X.2017.1334318