Efficacy and safety of pegvisomant in the treatment of acromegaly

Accepted 30th August, 2019

ABSTRACT

Pegvisomant, an inhibitor of growth hormone (GH) receptor, appeared as the best treatment for acromegaly. The objective of this study was to determine the efficacy and safety of pegvisomant in the treatment of acromegaly. A systematic review of randomized clinical trials was performed in the Brazilian Cochrane Center. Inclusion criteria included randomized controlled trials (RCTs); participants: patients with acromegaly; intervention: pegvisomant; comparison: other drug or placebo; types of outcomes: changes in IGF-1 and growth hormone; clinical and metabolic improvement; adverse effects; quality of life; exclusion criteria: clinical trials that did not meet the inclusion criteria. All searches conducted were without restriction language or dates. Search strategy: electronic: Lilacs, Medline, Pubmed, and Cochrane Central Library. The five studies included in this systematic review provide data for twenty-one analysis. No metanalysis was possible. The four comparisons performed with pegvisomant were pegvisomant versus placebo, pegvisomant versus somatostatin analog, pegvisomant versus the combination of pegvisomant + somatostatin analog and the combination of pegvisomant + somatostatin analog versus somatostatin analog. The most frequent outcome was normalization of IGF-1. The single outcome was positive changes in bone metabolism with the use of pegvisomant. The other outcomes aim at the quality of life and adverse events. Pegvisomant was effective and safe in reducing clinical manifestations and normalizing laboratory abnormalities of acromegaly alone or in combination with other drugs.

Key words: Acromegaly, pegvisomant, growth hormone, insulin-like growth factor 1, osteocalcin.

INTRODUCTION

Acromegaly

Acromegaly is a clinical syndrome resulting from increased secretion of growth hormone (GH), with or without pituitary adenoma. The diagnosis of acromegaly is built on clinical signs and symptoms, imaging (X-rays, CT scan or MRI) showing pituitary adenoma and serum concentrations of insulin-like growth factor 1 (IGF-1) one to three times the upper limit of the normal (ULN) rate. Although GH may have independent local effects, the majority of the somatic and metabolic effects of GH take place through the liver or local tissue production of IGF-1 (Ohlsson et al., 1998). GH
promotes bone development and its linear somatotrophic effects occur in part by stimulating the production of IGF-1. The IGF-1, produced primarily by the liver, circulates throughout the body, while the IGF-1 produced in the cartilage acts as a paracrine-autocrine growth factor. GH has anabolic and lipolytic effects and induces insulin resistance. The cardinal clinical features of acromegaly are bone growth leading to phenotypic characteristics and acceleration of acromegalic osteoarthrosis (Melmed, 1990) Clinical manifestations due to excessive concentrations of GH and IGF-1 are cardiovascular, cerebrovascular, respiratory and metabolic (Melmed et al., 1998; Harris, 1996; Giustina et al., 2000). The GH opposes the effects of insulin in the metabolism of carbohydrates (Clemmons, 2004) and glucose intolerance and diabetes mellitus are frequent complications reported in patients with acromegaly (Ezzat et al., 1994; Barrande et al., 2000; Mestron et al., 2004; Kreze et al., 2001; Fukuda et al., 2001).

So far, there are three main treatments for patients with acromegaly: surgery, radiation, and drugs. The surgery can cure acromegaly when removing the tumor completely, however, this is not always possible, especially if the tumor is large. The surgery solves 90% of cases of microadenomas and less than 50% of cases in macroadenomas (Sheppard, 2003).

Many patients with acromegaly have macroadenomas and need complementary treatment. Radiation therapy can decrease the secretion of GH but can take years to reduce the significant levels of the hormone, and can induce hypopituitarism since that radiates throughout the pituitary gland.

Pharmacological treatment is effective during his administration, but not able to induce a permanent cure. There are several drugs. The first drug used was somatostatin through subcutaneous applications three times a day. Later the same analogs with new technology began to have long-acting (octreotide LAR and lanreotide SR) that can be applied every seven or 28 days. The action in acromegaly is to inhibit the secretion of GH by activating receptors. There are five subtypes of somatostatin receptors, and the action of the analogs does not have the same power on all them, this is the reason why there are cases of acromegaly that respond poorly to therapy with somatostatin analogs (SA) (Freda, 2002). The decrease in GH levels and normalization of IGF-1 in patients with acromegaly improves glucose homeostasis. SA alter glucose homeostasis by inhibiting GH and insulin secretion (Bertoli et al., 1998; Ronchi et al., 2002; Parkinson et al., 2002; Baldelli et al., 2003; Quabbe and Plockinger, 1989). The action of SA outside the pituitary, particularly in the gastrointestinal tract, leads to many undesirable effects in patients with acromegaly (Lacranjan and Atkinson, 1999). Somatostatin has a complex effect on the neuroendocrine regulation of the gastrointestinal tract, because it inhibits the release of many peptides that regulate the intestine, blocking the pancreas exocrine function, stomach and bile, reducing gastric mobility and gastrointestinal transit time (Burroughs and McCormick, 1991). Pharmacological management of acromegaly can also be made by dopamine agonists. These drugs act directly at the pituitary by decreasing the secretion of GH and consequently reducing the levels of IGF-1 (Marzullo et al., 1999).

**Pegvisomant**

A great advance in the treatment of acromegaly was the introduction of pegvisomant (peg), an antagonist of GH, elaborated to prevent the activation of GH receptor, leading to a blockade of its effects and the reduction of IGF-1 (Fuh et al., 1992). This drug is an analog of growth hormone that prevents dimerization of the growth hormone receptor blocking cellular actions of the hormone after its binding, especially in the suppression of increased serum levels of IGF-1 (Pradhananga et al., 2002; Kopchick et al., 2002). The efficacy of peg in IGF-1 normalization does not depend on the presence of receptors, such as SA, and may have normalization of IGF-1 in almost all patients (Herman-Bonert et al., 2000; Parkinson and Trainer, 2001; van der Lely, 2002; Friend, 2002). As peg has no action on the secretion of GH, its use will lead to increased serum levels of GH, as a result of suppression of IGF-1. This can trigger an increase in the tumor, although this happened just in a few cases, and the indication of surgical treatment existed only in patients without prior radiotherapy (Trainer, 2002). The peg is an antagonist of GH receptor that does not affect insulin secretion. The drug peg has emerged as a therapeutic advance in the treatment of acromegaly because it supplements the deficiencies of SA for not acting in the production and secretion of growth hormone but act in its final action on the cellular level by blocking its receptors.

**METHODS**

**Setting and design**

A systematic review of randomized clinical trials was performed in the Brazilian Cochrane Center. Inclusion criteria: randomized controlled trials (RCTs); participants: patients with acromegaly; intervention: pegvisomant; comparison: other drug or placebo. Types of outcomes: changes in IGF-1 and GH; clinical and metabolic improvement; adverse effects; quality of life. Exclusion criteria: clinical trials that did not meet the inclusion criteria. All searches were done without language restriction or dates.

**Search for studies**

The electronic search was done with no language or date
restriction in the following databases: Lilacs, Medline (via PubMed), and Cochrane Library. A manual search carried out in medical journals in general and specific areas of neurology, neurosurgery did not add new studies to the electronic search.

Selection of studies and data collection:

Two reviewers independently inspected the references found by the search strategy, and applied the inclusion criteria in the selected studies. After observations of the description of the allocation concealment process of each study, it was classified into one of four categories: a) means that concealment of allocation was adequately reported b) means that concealment of allocation is not described but is mentioned that the study is randomized, c) that allocation concealment was inadequate, d) that the study is not random. We selected studies in categories a and b (Schulz et al., 1995).

Statistical analysis

For dichotomous variables, the relative risk (RR) with a confidence interval (CI) of 95% (random-effects model). When statistical differences, the number needed to treat (NNT) or number needed to harm (NNH) was calculated. For continuous variables, we calculated the weighted mean difference (random-effects model) with a range of 95% correspondingly. After finding all eligible studies, data were summarized in an analysis (one study) or metaanalysis (two or more studies) in the computer software RevMan of the Cochrane Collaboration (Review Manager, 2014). Five studies were included in this systematic review and allocation concealment in them was B for all.

Included studies

Trainer et al. (2000): 12-week, randomized, double-blind study of three different daily doses of pegvisomant [10 mg (n=26), 15 mg (n=26), and 20 mg (n=28)] and placebo (n=32), given subcutaneously, in 112 patients with acromegaly. Outcomes: measurement of serum growth hormone; measurement of serum IGF-I, adverse effects (Table 1).

Fairfield et al. (2002): 27 patients with acromegaly were randomized to daily subcutaneous injections of placebo (n = 7) or pegvisomant 10 mg (n = 7), 15 mg (n = 6) or 20 mg (n = 7). Outcomes: Serum markers of bone turnover after 12 weeks. Osteocalcin and carboxyterminal propeptide of type I procollagen (PICP) were measured as markers of bone formation and N-telopeptides of type I collagen (NTx) was measured as markers of bone resorption.

Ghigo et al. (2009): Multicenter, open-label, randomized study in 118 patients with acromegaly in 52 weeks. Fifty-six patients received pegvisomant and 57 received SA. The primary outcome was IGF-I normalization and secondary outcomes included mean changes from baseline in IGF-I, IGF binding protein 3, acromegaly quality of life questionnaire scores, and adverse effects.

Trainer et al. (2009): An open-label, multicentre, randomized, 40-week outpatient study. Twenty-five patients with suboptimally controlled acromegaly were randomized to pegvisomant and 26 to pegvisomant + somatostatin analog (SA). The primary outcome was adverse events (AEs) and the secondary was biochemical IGF-I-based efficacy.

Madsen et al. (2011): Eighteen well-controlled acromegalic patients on SA monotherapy were randomized in a 24-week monotherapy or unchanged co-treatment with pegvisomant (15 to 30 mg twice weekly) and somatostatin analogs (half the usual dose). Outcome Measures: Glucose tolerance, substrate metabolism, insulin sensitivity, body composition, and quality of life.

RESULTS AND DISCUSSION

The big target for those who are willing to do a systematic

Table 1: Characteristics of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Participation (N)</th>
<th>Treatment duration</th>
<th>Previous surgery (%)</th>
<th>Radiotherapy after surgery (%)</th>
<th>Radiotherapy without surgery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trainer 2000</td>
<td>Pegvisomant</td>
<td>Placebo</td>
<td>112</td>
<td>12 w</td>
<td>83.03</td>
<td>50.89</td>
<td>5.35</td>
</tr>
<tr>
<td>Fairfield 2002</td>
<td>Pegvisomant</td>
<td>Placebo</td>
<td>27</td>
<td>12 w</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Trainer 2009</td>
<td>Pegvisomant</td>
<td>Pegvisomant + SA</td>
<td>51</td>
<td>40 w</td>
<td>Yes, PU</td>
<td>Yes, PU</td>
<td>Yes, PU</td>
</tr>
<tr>
<td>Ghigo 2009</td>
<td>Pegvisomant</td>
<td>SA</td>
<td>113</td>
<td>52 w</td>
<td>NR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Madsen 2011</td>
<td>Pegvisomant + SA</td>
<td>SA</td>
<td>18</td>
<td>24 w</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR=Not reported, SA = Somatostatin analogue, W = week, PU = Percentage Unknown.
review is to find studies on the subject with similar goals, similar comparisons, and equal outcomes. All these with adequate follow-up are the ideal ingredients to be able to complete the systematic review with results and conclusions based on a meta-analysis. Unfortunately, this is not always possible. Although a comprehensive strategy was used in this systematic review, it was not possible to find studies with pegvisomant that could allow a meta-analysis to be performed. In view of this, the possible data from the randomized studies found were extracted, and isolated analyzes were performed. Two studies compared pegvisomant (peg) with placebo and another compared pegvisomant (peg) with a somatostatin analog (SA). Two other studies did a combined comparison of drugs, peg versus SA + peg, or peg + SA versus SA.

Comparison 1: Pegvisomant (peg) versus placebo (plac)

The analysis of Figure 1 shows that all doses of the peg (10, 15 and 20 mg) significantly reduced plasma concentrations of Insulin-like growth factor 1 (IGF-1), confidence interval (CI) -34.95 to -10.45, -57.94 to -34.26 and -68.36 to -48.64, respectively when compared with plac. As observed in this study, a reduction of IGF-1 is directly proportional to the dose of pegvisomant, while in the placebo group there are no appreciable changes. This shows that pegvisomant blocks growth hormone (GH) by preventing the production of IGF-1, the main mediator of the somatotrophic actions of this hormone (Figure 1) (Trainer et al., 2000).

The action of the peg as an antagonist of GH is in the cellular receptors. Therefore, the use of peg does not decrease but rather increases serum levels of GH in accordance with the dose and shows that the peg does not prevent GH secretion, like other drugs. Consequently, there was an increase of this hormone in the circulation, but without the metabolic and cardiovascular damage from its direct action at the cellular level, hampered by its antagonist peg. In comparison with the basal measurement, Figure 2 shows the change in serum levels of GH in three doses of peg versus plac. There was a slight decrease in serum GH in the plac group (-0.8 ± 5), while in the peg
group, there was an increase in serum GH proportionally to the dose of the peg. These results were statistically significant, CI 7.15 to 23.25 (20 mg), 5.56 to 14.44 (15 mg) and 0.75 to 6.25 (10 mg).

As would be expected from an effective drug versus placebo, the analysis in mean total score for individual signs and symptoms of acromegaly showed the improvement favorable to peg group. The signs and symptoms analyzed were soft-tissue swelling, excessive perspiration, fatigue, arthralgia, and headache. All differences were statistically significant, CI -6.48 to -1.12 (10 mg), -8.83 to -2.57 (15 mg), -8.74 to -3.26 (20 mg) (figure 3).

The mean decrease in ring size at 12 week was statistically significant for the peg group, CI 0.68 to 2.92 (15 mg) and 0.93 to 3.87 (20 mg). The peg 10 mg group had a reduction of 0.8 +/- 1.6, while in the placebo group had a reduction of 0.1 +/- 2.3 but not statistically significant probably for the short follow-up time (Figure 4).

Peg was well tolerated and although the incidence of adverse events was higher in all peg groups than in the placebo group, they were not statistically significant. The adverse effects analyzed were: upper respiratory tract infection, headache, injection site reaction, pain, diarrhea, flatulence, and nausea.

Acromegaly produces various morphological changes of
the skeleton and there is evidence of increased bone turnover in patients with acromegaly, as assessed by biochemical markers of bone resorption and formation (Halse and Gordeladze, 1981; de la Piedra et al., 1988; Halze and Gordeladze, 1978; Kotzmann et al., 1993). These abnormalities can be corrected or minimized by surgery of the pituitary and drugs (Takamoto et al., 1985; Eskildsen et al., 1979; Bijlsma et al., 1983; Levogini et al., 1997). A study conducted to measure these markers in patients with acromegaly treated with SA for 15 months found a significant reduction of osteocalcin, but not PICP (Terzolo et al., 1993). Another study in ten acromegalic patients who underwent transsphenoidal surgery showed normalization of osteocalcin (Marazuela et al., 1993). Fairfield et al. (2002) carried out a study, in twenty-seven patients with acromegaly as part of a multicenter, 12-week placebo-controlled trial investigating serum markers of bone turnover determined at baseline and at 12 weeks. Seven patients with acromegaly were randomized to daily subcutaneous injections of plac (n = 7) or peg 10 mg (n = 7), 15 mg (n = 6) or 20 mg (n = 7). Osteocalcin and PICP were measured as surrogate markers of bone formation and NTx were measured as surrogate markers of bone resorption. There was a statistically significant decrease in these markers in peg group: osteocalcin, CI -2.56 to -1.86 (p<0.00001); PICP, CI -52.07 to -31.33 (p<0.00001); NTx, CI -6.05 to -4.75 (p<0.00001). The pegvisomant, as an antagonist of the GH, blocks the production of IGF-1, significantly minimizing its somatotrophic effect, a marked clinical expression in acromegaly (Figure 5).

Comparison 2: Pegvisomant (peg) versus somatostatin analogs (SA)

The first multicenter randomized trial comparing two active drugs (peg and SA) for the acromegaly treatment, published by Ghigo et al. (2009) had a long follow-up of 52 weeks. The number of patients with IGF-1 normalization at week 52 was greater in the peg group (29) than in the SA group (19) but not statistically significant, CI: 0.96 to 2.34, RR 1.50. This led to the calculation of the risk difference (RD = 0.17) and the number needed to treat (NNT= 6). This data showed the superiority of peg, that is, for every six patients using SA that did not reach IGF1 normalization, one would benefit from the use of peg (Figure 6).

To ratify this superiority, this study measured IGFBP-3, which is the major carrier protein of IGF1 in the bloodstream, where it carries the growth factors predominantly in stable complexes that contain the binding protein. The mean (SD) decrease from baseline in IGFBP-3 at week 52 was statistically significantly greater with peg than with SA, CI 4.27 to 23.73, P= 0.005 (Figure 7). GH dosage at week 52 was significantly higher in the group peg, confirming its action on GH receptor, and not in their production. Mean GH levels increased significantly in

Figure 5: Biochemical markers of bone formation and resorption.

Figure 6: IGF-1 normalized after 52 week.
Figure 7: IGFBP-3, mean (SD) % change from baseline.

Figure 8: Changes in growth hormone (GH) levels at 52 week.

Figure 9: Effect of pegvisomant and SA on glucose levels in the oral glucose tolerance in fasting and after 120 min.

peg group and decreased in the SA group, CI: 14.11 to 38.89, P<0.0001 (figure 8).

Glycemic control was more effective in the pegvisomant group. There was a statistically significant reduction of glucose levels (mmol / l) in fasting and after 120 min in favor of pegvisomant group, CI -1.21 to -0.81 and -2.45 to -0.81 respectively, P=0.0001, at week 52 (Figure 9).

All adverse effects occurred more in the SA group, but without statistical significance when compared with the peg group, CI 0.47 to 1.09, P=0.12. The same happened with specific adverse effects such as increase AST, cholelithiasis, headache, and injection site reaction. Diarrhea was the only adverse effect with statistical significance favorable to the peg group, CI 0.07 to 0.75, P= 0.02. The outcomes Acromegaly Quality of Life (EUROQoL) Questionnaire, Acromegaly signs and symptoms, ring size were similar between the peg and SA groups. These data demonstrate that despite the different sites of action of drugs, regardless of the supremacy of pegvisomant in some items, both can control acromegaly.

Comparison 3: Pegvisomant (peg) versus the combination of SA + peg

Trainer and colleagues published an interesting study in 2009. They chose acromegalic patients using SA and who had not normalized IGF1 and randomized them to either use pegvisomant or continue SA with smaller doses of pegvisomant. At 40 weeks more than half of the patients had normalized IGF1 (14/25 and 16/26 patients in the group peg and in the combination therapy group respectively), CI 0.57 to 1.44, P= 0.69.

The outcomes quality of life and the signs and symptoms of acromegaly improved in both groups. In the adverse effects outcome, there was an increase in liver
Elevated hepatic transaminase level (> 3 x ULN) affecting four patients in the combination therapy group and one patient in the peg monotherapy group. There was no statistically significant difference between the groups, CI 0.03 to 2.17, P=0.21.

At week 40, there was a statistically significant decrease in mean (SD) level of HbA1c in the pegvisomant monotherapy group, CI -0.51 to -0.03, p=0.03 showing the beneficial effect of pegvisomant on diabetics (Figure 10).

Comparison 4: The combination of pegvisomant (peg) + SA versus SA

Madsen et al. (2011) randomized well-controlled acromegaly patients with SA monotherapy to migrate to the use of peg combined with half-dose SA or SA maintained with the previous dose. They did not find a statistically significant difference between the groups in the outcomes analyzed: serum level of IGF1, quality of life, glycemic levels, levels of hormones and metabolic parameters. The study had a follow-up of 22 weeks with few participants. In the analysis of the results, it has to be taken into account that all participants started the study compensated previously.

Important non-randomized studies with pegvisomant have been conducted in the last decades. The outcomes of 792 patients with acromegaly were published in ACROSTUDY, an international observational web-based patient registry. The patients taking pegvisomant (15 mg daily) had a mean follow up of 20 months and IGF-1 levels normalized in 62% of patients. IGF-1 did not differ significantly as compared with the monotherapy, regardless of whether the patient was receiving other treatments for acromegaly, such as dopamine agonists or somatostatin analogs (Trainer, 2009).

The GPOS (German Pegvisomant Observational Study) was an observational multicenter study to monitor the efficacy and safety of pegvisomant. It started in January 2004 and was until August 12th, 2008 (protocol was similar to the protocol of ACROSTUDY) with 371 patients with acromegaly enrolled in the study. In 71.3% of patients with previously not sufficiently treatable acromegaly, IGF1 levels normalized by pegvisomant therapy for up to five years of treatment. Elevated transaminases usually normalized after discontinuation and tumor progression was a rare event (Buchfelder, 2009).

A systematic review published in 2009 included only one randomized-controlled trial plus 17 non-randomized studies. The methodological quality of the included studies was poor or could not be determined and a meta-analysis did not exist because the review was more narrative. It ended that pegvisomant is effective for improving patients’ IGF-1 level, but an economic evaluation of cost-effectiveness applied to pegvisomant did not show reasonable values (Moore, 2009).

A report done in 2011 by North East Treatment Advisory Group (NETAG) agrees to the economic evaluation made by the systematic review of 2009 and said that pegvisomant may be used as monotherapy initially, although published experience from clinical studies shows that it may be used in combination with other pharmacological therapies, particularly somatostatin analogs (Horsley, 2011).

CONCLUSION

In this systematic review, pegvisomant was effective and safe in reducing clinical manifestations and normalizing laboratory abnormalities of acromegaly alone or in combination with other drugs.

Implications for practice

Pegvisomant may be indicated for all patients in the treatment of acromegaly. When there is economic hardship, it should be performed in patients resistant to somatostatin analogs and dopamine agonists, and in patients whose adverse effects of the latter drugs require alternative treatment.

Implications for research

The high technology of this medicine, its odd mode of action does not require further research.

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