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Systematic Review

Medical Treatments for Acromegaly: A Systematic Review and Network Meta-Analysis

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ABSTRACT

Background: Acromegaly results from the hypersecretion of growth hormone. Because of the low incidence rates of this disease worldwide, few clinical trials evaluating drug treatments have been conducted. **Objectives:** To conduct the first network meta-analysis simultaneously comparing all available drugs used in acromegaly treatment so as to provide more robust evidence in this field. **Methods:** A systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Cochrane Collaboration recommendations (PROSPERO database under the registration number CRD42017059880). The electronic searches were conducted in PubMed (MEDLINE), Scopus, and Web of Science databases. Randomized controlled trials comparing any drug for the treatment of acromegaly head-to-head or versus placebo were included. Outcomes concerning the efficacy and safety of treatments were evaluated. The statistical analyses were performed using Aggregate Data Drug Information System version 1.16.8 (drugis.org, Groningen, The Netherlands). **Results:** The initial search retrieved 2059 articles. Of these, 10 randomized controlled trials were included in a qualitative analysis and 7 in a quantitative analysis. The network meta-analysis for the efficacy outcome (number of patients achieving insulinlike growth factor 1 control) showed that pegvisomant and lanreotide autogel were statistically superior to placebo (odds ratio [95% credible interval] 0.06 [0.00–0.55] and 0.09 [0.01–0.88]). No further differences were found. The probability rank indicated that pegvisomant and pasireotide have the highest probabilities (33% and 34%, respectively) of being the best therapeutic options. No major side effects were noted. **Conclusions:** Pegvisomant is still a good option for acromegaly treatment, but pasireotide seems to be a promising alternative. Nevertheless, other important key factors such as drug costs and effectiveness (real-world results) should be taken into account when selecting acromegaly treatment.

Keywords: acromegaly, meta-analysis, network meta-analysis, pasireotide, pegvisomant, pituitary gland.

Introduction

Acromegaly is a rare disease resulting from growth hormone (GH) hypersecretion, usually caused by a pituitary adenoma [1]. According to recent studies, there are between 14 and 85 cases of acromegaly per million people worldwide, and the incidence is approximately 1 to 11 cases per million per year across the world [2–4].

Because it is a slowly developing disease, the clinical manifestations of acromegaly, such as enlargement of the hands and feet and coarse facial features, may be confused with signs of aging or other diseases [5]. Therefore, patients with acromegaly normally take from 8 to 10 years to receive a correct diagnosis, leading to the appearance of complications such as cardiovascular, respiratory, and neoplasia problems that are responsible for an increase in mortality [6].

Disease control is achieved when normal levels of GH and insulinlike growth factor 1 (IGF-1) are attained in blood [7,8]. The treatment modalities currently available are surgery, radiotherapy, and drug therapy. Trans-sphenoidal surgery is the first-line intervention for the treatment of acromegaly. Nevertheless, because it is often not possible to remove the entire pituitary tumor through surgery (success rates of 40%–80%) [5,9,10], pharmacological treatments are needed. Moreover, drug therapy is also used when surgery is not recommended or when the patient refuses to undergo surgical procedures. The drug options for

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controlling GH and/or IGF-1 levels are dopaminergic agonists (bromocriptine and cabergoline), somatostatin analogs (lanreotide, octreotide, and pasireotide), and the GH receptor antagonist pegvisomant [11].

Because acromegaly is a rare disease, few randomized controlled trials (RCTs) have been published so far. Likewise, until now no systematic review with a meta-analysis has been performed to compare all medical treatment classes used to control acromegaly. With the advent of network meta-analysis, which evaluates direct and indirect evidence simultaneously, a broader set of available therapeutic options can be built, enabling conscious decision making [12]. Therefore, we conducted a systematic review with network meta-analysis of RCTs to assess and compare the efficacy and safety of drugs used in the treatment of acromegaly.

Methods

Eligibility Criteria for the Systematic Review

A systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Cochrane Collaboration recommendations [13,14]. The study protocol was published in the PROSPERO database under the registration number CRD42017059880. Two independent reviewers conducted all the steps and compared the data. Any discrepancy was resolved by a third reviewer.

RCTs involving patients with acromegaly were identified using PubMed, Scopus, Web of Science, and Scielo. A manual search in the references of the included studies was also performed. The search was conducted in April 2017 with no date restriction. The search strategies encompassed the following descriptors: "clinical trial," "random*," "acromegaly," "octreotide," "lanreotide," and "pegvisomant," among others, combined with Boolean operators AND and OR. The complete search strategies can be seen in Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2017.12.014.

Studies were included if they met all the following eligibility criteria: 1) patients diagnosed with acromegaly, 2) head-to-head or versus placebo RCTs involving any drug used in the treatment of acromegaly, and 3) studies should report any efficacy outcome: IGF-1 control and/or GH control or any safety outcome related to adverse events (AEs).

Studies that did not address outcomes of interest, other types of studies (such as cohorts, case reports, and reviews), non-RCTs, and articles published in non-Roman characters were excluded.

Data Extraction and Quality Assessment

The following data were extracted from each study: data concerning the evaluated treatment (dosage, route of administration, and treatment duration), baseline data (number of patients, sex, age, and previous treatments), efficacy data (GH and IGF-1 values before and after treatment and the number of patients with GH and IGF-1 control), and safety outcomes (number of AEs and AEs leading to treatment discontinuation).

The Jadad Scale [15] and the Cochrane Collaboration's tool for assessing the risk of bias [13] were used to assess the methodological quality of studies included in this systematic review. Important factors that can bias clinical trials are evaluated through these tools, including randomization and blinding. The Jadad tool consists of a numerical scale in which the maximum score is 5 [15]. The Cochrane Collaboration's tool is a more detailed tool and classifies each study as having a low, unclear, or high risk of bias [13].

Statistical Analyses

Network meta-analysis combines direct and indirect evidence, making feasible the comparison of treatments that would not be possible by pairwise meta-analysis [16]. Usually based on Bayesian methods, this approach is recommended by the International Society for Pharmacoeconomics and Outcomes Research for comparing efficacy and safety among different treatments [17].

We created a random effects model using the Markov chain Monte-Carlo simulation method to generate pooled effect sizes. A consistency model was built for each outcome, and the relative effect size for each treatment was calculated as the odds ratio (OR) and reported with 95% credible interval (CrI). We assumed a common heterogeneity parameter. Our model adopted a random effects model rather than a fixed effects model because it is perhaps the most appropriate and conservative analysis to account for variance among studies. The goodness of fit of the model was assessed using residual deviance. A probability rank was also built. This rank estimates the probability that each drug is the best, second best, and so on, concerning each outcome. The treatments were ranked by the surface under the cumulative ranking curve [18,19].

To ensure that there are no divergences between direct and indirect comparisons and to estimate the robustness of the network, a node-splitting analysis was performed (P values less than 0.05 indicate inconsistencies) [20,21]. To be consistent with the treatment arms provided by the included studies and avoid the occurrence of potential biases, the geometry of the treatment network under study followed the complexity level of the reports of the primary studies included in the present meta-analysis. A subanalysis considering studies that used medical treatment as primary and secondary therapy was performed.

The analyses were performed using Aggregate Data Drug Information System version 1.16.8 (Groningen, The Netherlands) [22].

Results

The systematic search retrieved a total of 2059 articles, of which 561 were excluded as duplicates. After screening the 1498 remaining articles for their title and abstract, the full text was evaluated for 37 studies. Of these, 10 RCTs [23–32] were included in the systematic review. All 10 studies composed the qualitative analysis. Seven of the 10 [23,25–27,30–32]were also suitable for quantitative analysis (network meta-analysis) (n = 801; Fig. 1). Three studies were not included in the meta-analysis because they did not assess the outcome of interest of the network: number of patients who achieved IGF-1 control.

Study Characteristics

The main characteristics of the 10 studies included in the systematic review are presented in Table 1. The studies encompassed the drugs bromocriptine, lanreotide (sustained release formulation), lanreotide autogel (extended release formulation), octreotide, octreotide long-acting release (LAR), pasireotide, pegvisomant, and placebo. The doses were not fixed and usually could be titrated according to the patients' biochemical responses, similarly to what happens in the real world. The frequency of administration depended on drug formulation, and treatment duration ranged from 1 to 13 months. Just 1 of the 10 RCTs specified that only surgery-naive patients could be enrolled [23]. Three of the studies used a crossover design [24,25,29]. The proportion of men and women was comparable in the studies and among the studies.

The trials enrolled, overall, few patients because acromegaly is a rare disease. The largest trial is the one from Colao