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Original Article

Cost-effectiveness analysis of preoperative treatment of acromegaly with somatostatin analogue on surgical outcome

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ABSTRACT

Context: There is no uniform standard of care for acromegaly. Due to the high costs involved, steps must be taken to ensure the cost-effective delivery of treatment.
Objective: Taking the results of an earlier meta-analysis as a starting point, this study aims to determine whether treatment with long-acting somatostatin analogue (SSA) prior to surgery improves the cost-effectiveness of the treatment of acromegaly.
Methods: The results are presented as an Incremental Cost Effectiveness Ratio (ICER) immediately after surgery, for the following year and over the next four decades. The cure rates percentage (95% CI) for the three randomized prospective controlled trials were 44.4% (34.2–54.7) and 18.2% (10.1–26.3) for preoperative treated and untreated patients respectively. The cost of pharmacological treatments was based on the number of units prescribed, dose and length of treatment.
Results: The mean (95% CI) ICER immediately after surgery was €17,548 (12,007–33,250). In terms of the postoperative SSA treatment, the ICER changes from positive to negative before two years after surgery. One decade after surgery the ICER per patient/year was €−9973 (−18,798; −6752) for postoperative SSA treatment and €−31,733 (−59,812; −21,483) in the case of postoperative pegvisomant treatment.
Conclusions: In centres without optimal surgical results, preoperative treatment of GH-secreting pituitary macroadenomas with SSA not only shows a significant improvement in the surgical results, but is also highly cost-effective, with an ICER per patient/year one decade after surgery, of between €−9973 (−18,798; −6752) and €−31,733 (−59,812; −21,483) for SSA and pegvisomant respectively.

1. Introduction

Acromegaly is a severe but rare disease due, in the vast majority of cases, to GH-secreting pituitary adenomas (approximately 98%). The incidence of acromegaly stands at around 5 cases per million per year and the prevalence is 60 cases per million [1]. Current treatment for acromegaly includes neurosurgery, radiotherapy and medical therapy with somatostatin analogue (SSA), dopamine agonists and the GH-receptor antagonist pegvisomant [1–6]. There is no uniform standard of care for acromegaly. Furthermore, and due to the high costs involved, steps must be taken to ensure the cost-effective delivery of treatment [7,8]. In all studies medical treatment is the largest contributor to the total cost of acromegaly management [9].

In the majority of patients, transsphenoidal neurosurgery is the accepted first-line treatment for acromegaly [6]. Maximum reported cure rates for microadenomas and macroadenomas stand at between 80–90% and 50–60% respectively [10,11]. In the Belgian registry on acromegaly, a survey of "real life" outcome in 418 acromegalic subjects, the surgical cure rate by definition of both normal IGF for age and GH < 2 μg/l was 34% [12]. In the German registry on acromegaly, made up of 1344 patients, the surgical cure rate, defined by a normal IGF-I, was 38.8%[13]. Overall cure rates as low as 18% (39% microadenomas and 12% macroadenomas) have been reported [14]. It is possible that other studies registering low cure rates remain unpublished.

SSA treatment may cause shrinkage of GH-secreting pituitary adenomas [2]. In theory, this could improve the likelihood of a radical resection. Furthermore, it has been suggested that SSA treatment softens the tumour parenchyma and thereby facilitates tumour removal [15,16]. It has also been reported that SSA pre-treatment leads to a shortening of postoperative hospital stay [17]. Previous studies addressing preoperative

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SSA treatment and subsequent surgical cure rates are conflicting, reporting benefits [16–21] or no difference when compared with preoperative SSA treatment [15,22–27]. The guidelines issued by the American Association of Clinical Endocrinologists, posit a role for presurgical medical therapy with SSA to improve biochemical outcomes with surgery [28]. However, this is a highly controversial issue and further studies are needed to support its general use [28,6]. Moreover, to date, there is insufficient evidence to recommend it for improved surgical outcome or a reduction in postoperative complications [8]. Nevertheless, a recently published meta-analysis of preoperative treatment of GH-secreting pituitary adenomas with SSA on surgical outcome has revealed a significant improvement in surgical results [29].

Taking the results of an earlier meta-analysis as a starting point, this study aims to determine whether treatment with long-acting SSA prior to surgery improves the cost-effectiveness of the treatment of acromegaly.

2. Methods

2.1. Study design

We investigated the impact of treatment with SSA prior to surgery on the cost-effectiveness of acromegaly treatment. The outcome variable was reported as biochemical control rates in patients with preoperative SSA treatment versus no preoperative treatment, and the costs of both strategies were compared. The economic analysis includes the three randomized prospective controlled clinical trials with long-acting SSA currently used in acromegaly treatment and which have been previously included by our group in a meta-analysis [29]. The postoperative biochemical control criteria were defined, as age adjusted normal IGF-I and fasting GH of less than 2.5 μg/L or GH after oral glucose tolerance test of less than 1 μg/L. The results are presented as an Incremental Cost Effectiveness Ratio (ICER) of preoperative treatment in the immediate postoperative period ($ICER_1$), one year after surgery ($ICER_{2a}$) and several decades after surgery($ICER_{2b}$), considering persistent pharmacological treatment in the patients that were not cured by surgery [30].

2.2. Perspective

This study was carried out within the context of the Spanish National Health Service. Only the direct costs of pharmacological treatment using the most effective drugs approved for acromegaly treatment, namely SSA (octreotide or lanreotide) and pegvisomant, were taken into consideration.

2.3. Time period

The time periods considered were the immediate postoperative period ($ICER_1$), considering pharmacological preoperative costs with SSA only; one year after surgery ($ICER_{2a}$), considering pharmacological preoperative costs with SSA, and persistent pharmacological treatment in the patients that were not cured by surgery (both the preoperative treated and the control group) with the presently approved drugs (SSA and pegvisomant); and one to forty years after surgery ($ICER_{2b}$) considering pharmacological preoperative costs with SSA and persistent pharmacological treatment in the patients not cured by surgery (both the preoperative treated and control group) with the currently approved drugs (SSA and pegvisomant). The results are presented in decades 1–10, 11–20, 21–30 and 31–40 years.

2.4. Clinical efficacy

The economic analysis includes the three randomized prospective controlled clinical trials with long-acting SSA that are currently in use for acromegaly treatment (Table 1) and which have previously been included by our group in a meta-analysis [29]. In the trials carried out by Shen et al. [26] and Carlsen et al. [18] octreotide long-acting release (LAR) was used: 20 mg im was administered every 28th day for 3 months and 20 mg im every 28th day for 6 months, respectively. The study by Mao et al. [19] used lanreotide slow-release (SL), starting with 30 mg/2 weeks im and increasing to 30 mg/week im at week 8 if mean GH >2.5 μg/L on GH day curves, the total duration of treatment was 16 weeks. The differences in cure rates between treatment groups in the prospective trials are shown in Fig. 1. Treatment effectiveness was significant, with a pooled OR (random effects) for biochemical cure with SSA treatment of 3.62 (95% CI, 1.88–6.96). The mean (95% CI) cure rate for the three randomized prospective controlled trials was 44.4% (34.2–54.7) and 18.2% (10.1–26.3) for preoperative treated and untreated patients respectively.

2.5. Cost analysis

The study considered only the direct costs of pharmacological treatment based on the number of units required, prescribed dose and length of treatment with respect to the ex-factory price of each unit. The preoperative treatment considered was those used by the three prospective controlled trials, octreotide LAR 20 mg im every 28th day for 3 months [26] and 20 mg im every 28th day for 6 months [18] and lanreotide SL 30 mg every 1 or 2 weeks im for 16 weeks [19]. The postoperative treatment considered for those patients not cured by surgery was that approved by the National Health Authority (Spanish Medicines Agency) and the most frequently used: octreotide LAR (sandostatin LAR®) 20 mg im every 28th day, lanreotide SL (somatulin Autogel®) 90 mg every 28th day or pegvisomant (somavert®) 15 mg/day [9].

The cost of the pharmacological treatments was obtained from the Official General Pharmaceutical Association of Spain Bot PLUS 2.0 database (https://botplusweb.portalfarma.com/) (Table 2). All resources were calculated in euros.

2.6. Discount rates

The discount rate applied to estimate the $ICER_{2a}$ and $ICER_{2b}$ was 2.111% for the first decade, 2.679% for the second decade and 2.715% for the third and fourth. These were based on the Bank of Spain's reference rate for estimating market value in compensation for interest rate risk on mortgage loans.

2.7. Statistical and pharmacoeconomic analysis

The results are expressed as mean (SD), median and range, absolute values and percentages (95% CI). The main outcome of interest was the percentage of postoperative biochemical cure rate in both preoperatively treated and non-treated patients. Pharmacoeconomic estimates were based on the odds ratio (OR) and absolute risk reduction (ARR) between both groups of patients, with 95% confidence interval, used as measures of association and obtained from the meta-analysis from Pita-Gutierrez and col [29]. We estimated the number needed to treat (NNT) from the ARR (NNT = 1 / ARR). Incremental cost-effectiveness ratios (ICERs) were calculated as the product of cost difference between therapeutic alternatives analysed and the number of patients needed to treat (NNT). Data were analysed by EPIDAT 3.1 software (Xunta de Galicia/PHO, A Coruña, Galicia, Spain, 2006). All reported p-values are two sided, with the significance p value set at $p < 0.05$.

2.8. Sensitivity analysis

A sensitivity analysis was carried out using the limits of the 95% confidence interval of the number needed to treat, considering the worst value for treated patients and the best value for the control group.