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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.

Keywords

Acromegaly; Cost-effectiveness analysis; Preoperative; Treatment

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], [2], [3], [4], [5] and [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] and [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] and [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] and [16]. It has also been reported that SSA pre-treatment leads to a shortening of postoperative hospital stay [17]. Previous studies addressing preoperative SSA treatment and subsequent surgical cure rates are conflicting, reporting benefits [16], [17], [18], [19], [20] and [21] or no difference when compared with preoperative SSA treatment [15], [22], [23], [24], [25], [26] and [27]. The guidelines issued by the American Association of Clinical Endocrinologists, posit a role for pre-surgical 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] and [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.

Table 1. Percentage of postsurgical biochemical cure in the randomized prospective controlled trials of pre-operative treatment of acromegaly with somatostatin analogue on surgical outcome.

Author	Group	n	Cured	Not cured	P	Cured (95% CI)	Not cured (95% CI)	OR (95% CI)
Carlsen M	Treated	31	14	17	0.11	45.2% (26.0–64.3)	54.8% (35.7–74.0)	2.7 (0.9–8.1)
	Control	30	7	23		23.3% (6.5–40.1)	76.7% (59.9–93.5)	
Shen M	Treated	19	6	13	0.13	31.6% (12.6–56.6)	68.4% (43.5–87.4)	4.4 (0.7–23.9)
	Control	20	2	18		10.0% (1.2–31.7)	90% (68.3–98.8)	
Mao Z-g	Treated	49	24	25	0.001	49.0% (34.0–64.0)	51.0% (36.0–66.0)	4.3 (1.7–10.6)
	Control	49	9	40		18.4%(6.5–30.2)	81.6% (69.8–93.5)	

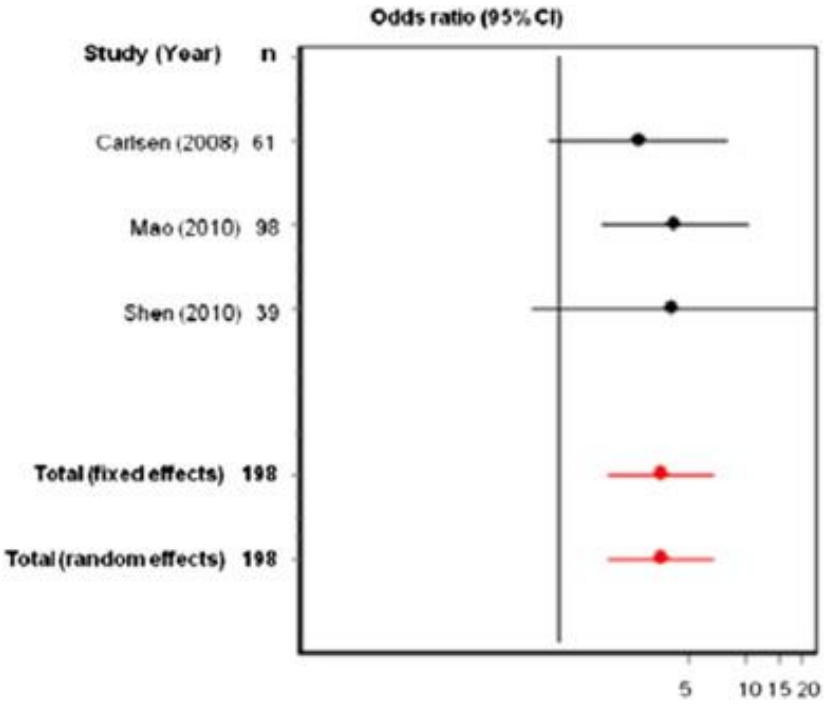

Fig. 1. Forest plot of randomized prospective controlled trials of preoperative treatment of acromegaly with somatostatin analogue on surgical outcome.

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.

Table 2. Generic drugs, brand name and Laboratory Sale Price (SP).

Generic drugs	Brand name	SP (€)
Octreotide	Sandostatin (1 mg, 1 blister)	21.71
	Sandostatin (100 mcg, 5 blisters)	10.85
	Sandostatin (50 mcg, 5 blisters)	5.43
	Sandostatin LAR (10 mg, 1 blister)	780.89
	Sandostatin LAR (20 mg, 1 blister)	1023.04
	Sandostatin LAR (30 mg, 1 blister)	1265.17
Lanreotide	Somatulin (30 mg, 1 blister)	435.67
	Somatulin Autogel (120 mg, 1 prefilled syringe)	1240.56
	Somatulin Autogel (60 mg, 1 prefilled syringe)	766.03
	Somatulin Autogel (90 mg, 1 prefilled syringe)	1003.29
Pegvisomant	Somavert (10 mg, 30 blister)	2079.28
	Somavert (15 mg, 30 blister)	3089.85
	Somavert (20 mg, 1 blister)	188.4
	Somavert (20 mg, 30 blister)	4100.42

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.

3. Results

3.1. Direct costs

The cost of preoperative treatment per patient with octreotide was between €3069 and €6138 for 3 or 6 months of treatment respectively. The cost of preoperative lanreotide treatment was €4447. The mean cost of SSA preoperative treatment was €4618 per patient.

The cost of 1 year of postoperative treatment for a patient not cured after surgery depends on the type of postoperative treatment employed: €13,043 in the case of lanreotide, €13,300 for octreotide (€13,172 mean cost for SSA) and €37,595 for pegvisomant.

Fig. 2 shows the decision tree for acromegaly treatment in this pharmacoeconomic study, including the corresponding pre-surgical therapeutic options, mean response rate and associated cost during the first year.

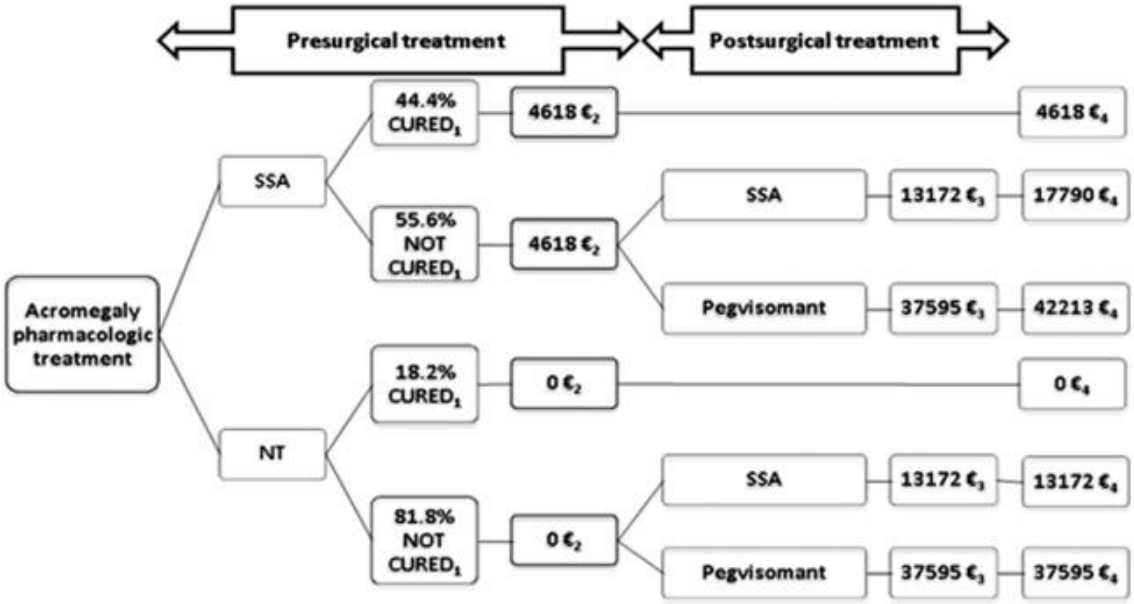

Fig. 2. Decision tree for acromegaly treatment in this pharmacoeconomic study, including corresponding presurgical therapeutic options, mean response rate and associated cost during the first year. Somatostatin analogue (SSA). No treatment (NT). 1. Mean cured or not cured percentage after surgery. 2. Mean cost/patient of presurgical treatment. 3. One year mean cost/patient of postsurgical treatment. 4. One year mean cost/patient of pre-surgical and postsurgical treatment.

The mean cost per patient/year for the postoperative treatment of patients not cured after surgery, applying the discount rate, stood at between €5426 and € 11,736 for SSA treatment and between €15,485 and €33,495 for pegvisomant treatment, during the fourth and first decades respectively.

3.2. $ICER_1$

Table 3 shows the Incremental Cost Effectiveness Ratio of preoperative treatment in the immediate postoperative period ($ICER_1$) for the three prospective randomized studies and meta-analysis from Pita-Gutierrez et al. [29].

Table 3. Incremental Cost Effectiveness Ratio (ICER) of preoperative treatment in the immediate postoperative period ($ICER_1$) for the three prospective randomized studies and meta-analysis from Pita et al. Absolute risk reduction (ARR). Number needed to treat (NNT).

Author	ARR	NNT	Cost/patient	$ICER_1$
Carlsen M	21.8% (− 1.3–45.0)	4.6 (− 75.6–2.2)	€6138	€28,238
Shen M	21.6% (− 3.1–46.3)	4.6 (− 32.1–2.2)	€3069	€14,117
Mao Z-g	30.6% (12.9–48.3)	3.3 (2.1–7.7)	€4447	€14,675
Pita-Gutierrez F	25.9% (13.7–38.2)	3.8 (2.6–7.2)	€4618	€17,548

The global ICER (95% CI) of preoperative treatment in the immediate postoperative period ($ICER_1$) for the three prospective randomized studies was €17,458 (12,007–33,250)/patient. These data support the sensitivity analysis, considering a threshold for annual ICER of $50,000/patient (€36,500/patient).

3.3. $ICER_{2a}$

The global ICER (95% CI) of treatment including pre- and post-surgical costs, considering the first year of postsurgical treatment ($ICER_{2a}$) was €4454 (3016–8396)/patient for SSA treatment and €− 19,969 (− 37,640; − 13,519)/patient in the case of treatment with pegvisomant. Both therapeutic strategies are cost-effective, as neither exceeds the threshold of $50,000/patient (€36,500/patient). Furthermore, the non-use of pegvisomant in the patients cured with SSA pre-treatment means direct savings of around €20,000/patient.

3.4. $ICER_{2b}$

Fig. 3 indicates the global ICER (95% CI) of treatment for biochemical remission including pre- and post-surgical costs, considering the four decades of postsurgical treatment. It reveals that pre-operative SSA treatment represents a significant opportunity cost, with direct savings for all the decades analysed.

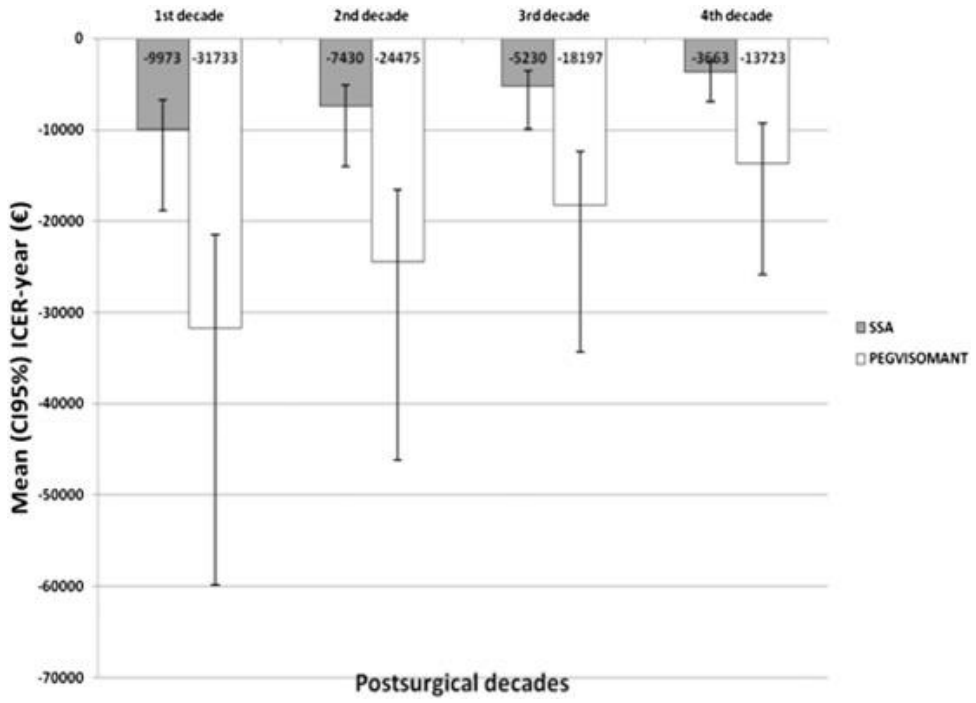

Fig. 3. Mean (95% C.I.) Incremental Cost Effectiveness Ratio-year (ICER-year) in euros of treatment for biochemical control including pre-surgical and postsurgical costs, considering the four decades of postsurgical treatment ($ICER_{2b}$) for postoperative SSA.

When considering SSA postoperative treatment, the change from positive ($ICER_{2a}$) to negative ($ICER_{2b}$) ICER occurs between the first and second year after surgery. This means that prior to two years after surgery, pre-operative treatment with SSA involves direct savings in treatments with drugs. Due to the chronic characteristics of acromegaly, this saving increases significantly 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 (Fig. 3).

4. Discussion

Based on a previous meta-analysis and taking into account economic aspects, we have found that pre-operative treatment with SSA of GH-secreting pituitary macroadenomas, not only leads to a significant improvement in surgical results, but is also extremely 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.

The outcome of treatment with SSA as primary or secondary therapy in clinical practice has been reviewed by Colao et al. [2], controlling excess GH in 60–62% of patients with normalization of IGF-I levels in 59–49% of patients. Tumour shrinkage was observed in 56–75% of patients treated with SSA [2]. A meta-analysis has found that octreotide LAR induces clinically relevant tumour shrinkage in more than half of patients with acromegaly, and that intramuscular octreotide LAR produced tumour shrinkage in twice as many patients as subcutaneous octreotide [31]. A recent study with lanreotide autogel 120 mg as primary therapy in acromegaly found that clinically significant tumour volume reduction at 48 weeks was achieved in 62.9% of 89 patients [32]. It has been found that pre-surgical SSA therapy not only lowers GH and IGF-1 concentrations and induces tumour shrinkage but also ameliorates or reverses cardiac, vascular, and sleep-related complications in many patients with acromegaly [33]. Certain clinical data suggest that the main reason for the improved surgical outcome in the treated group was that drug pre-treatment made some of the tumours less invasive [26]. However, other mechanisms that could modify the biology of the GH-secreting pituitary tumour cannot be excluded [34]. In somatotroph adenomas, immunohistochemical analysis has shown that somatostatin receptors 2 expression correlated with the response to octreotide and was reduced after octreotide treatment [35]. Nevertheless, from a clinical perspective, long-term treatment with SSA proves to be effective in acromegalic patients [36].

Moreover, the mean GH and IGF-1 continued to decrease over 10 years [36]. We have not included adjuvant radiotherapy in our cost-effectiveness study because it takes many years to normalize GH/IGF-I (more than 6 years in most patients), and leads to complications such as hypopituitarism in more than 50% of patients, brain necrosis, vascular damage, secondary neoplasia and cognitive impairment [37] and [38]. Radiotherapy is currently considered a third line therapy, for recurring or post-surgery persistent tumours, as well as for patients resistant or intolerant to medical treatment [6] and [8]. Cabergoline is not included in our analysis as it is not an approved treatment for acromegaly in Spain. Furthermore, it is less effective than SSA and is normally used as a third line treatment in combination with SSA [8] and [28].

Various studies have been carried out to assess the cost of illness with treatment for acromegaly [39], [40], [41], [42], [43] and [44]. In 2004, Didoni et al. carried out a retrospective study on direct costs in 134 patients over a 7 year period [39]. The costs of hospitalization, specialist costs, drugs for acromegaly and drugs for comorbidities were €7968 per year for controlled patients and €12,533 per year for non-controlled patients. Luque-Ramirez et al. studied costs in 11 consecutive patients with an invasive macroadenoma [40] in 2007 ranging from €7072 to €9874 per patient per year. Wilson et al. studied the costs of treatment in a total of 53 Canadian patients with acromegaly, with a mean follow-up of 49 months [41]. The mean annual cost per patient was $8111 in 2001. Valentim et al. undertook a cost–effectiveness analysis of octreotide LAR and lanreotide SR from the Brazilian perspective. They concluded that the use of octreotide LAR resulted in cost saving compared with lanreotide SR [42]. Roset et al. studied the costs of treatment for a total of 74 Spanish patients with acromegaly between 2005 and 2007; the mean annual cost of acromegaly was €9668 per patient. The cost of a patient treated with surgery only was €2501 year, compared with €9745 for a patient receiving only pharmacological treatment. In cases where a combination of both types of treatment is required, total annual costs range from €10,866 to €12,364. In all the studies considered, medical treatment is the largest contributor to total costs. It has been estimated that pharmaceutical treatment could represent up to 71% of the direct costs of the disease [43]. Moore et al. carried out a systematic review and economic assessment of pegvisomant, concluding that despite the high level of clinical effectiveness, it was not cost-effective [44]. However, comorbid costs of uncontrolled patients are higher than those of controlled patients [39] and [43]. The majority of studies failed to make proper comparison of the therapies and other relevant direct and indirect costs were not analysed [9]. The comparison between our study and previous ones is hindered by the fact that it was carried out in 2014 and only pharmaceutical costs were considered.

A key factor in the analysis of the global costs of acromegaly is biochemical control. The cost of acromegaly management is notably reduced when strict control criteria [45], with the aim of improving the survival of affected patients, are applied [46]. In this sense, the possibility of concentrating patient management in leading centres that obtain the best results would facilitate and increase the treatment success rate, without increasing economic costs. Alternatively our proposal for SSA pre-treatment has demonstrated its efficacy mainly in less experienced centres [29]. Regression analysis of the cure rates in untreated patients versus the odds ratio of the pre-treatment effect revealed a highly significant linear relationship (Spearman's Rho = − 0.842, $P < 0.0001$). These data indicate that centres with good surgical results do not benefit from pre-treatment and centres with worse surgical results benefit most from pre-treatment [29]. This study did not evaluate primary medical therapy; SSA can be prescribed as first line therapy for patients with invasive tumours without mass effects and a low probability of surgical cure as well as for those with contra-indications for surgery. In recent years a growing trend towards more and more primary treatment has emerged in a number of European countries [47], contrasting with the American approach that considers surgery to be the first-line treatment [6] and [28]. Although the benefits of acromegaly disease control are well known, many questions regarding the benefits of controlled compared with uncontrolled disease regarding the dimensions of morbidities, health-related quality of life, and non-pharmacological costs are posed. This study was carried out from the perspective of the Spanish National Health Service, although we believe it is applicable to any country.

The present study has several limitations. Its results are based mainly on prospective studies in patients with macroadenoma [19], [22] and [26], and are not applicable to microadenoma patients. In the study by Carlsen et al. [18], pre-surgical treatment clearly did not improve the surgical results in microadenoma patients. Our data must take into account that at diagnosis, about 75 percent of patients have macroadenomas [48]. Consequently these calculations should be applied only to this 75% of patients with acromegaly that bear a macroadenoma. The main limitation of the present study is the length of the postoperative evaluation period of the three studies included in the previous meta-analysis. Ideally, the period should be 1 year after SSA withdrawal, in order to exclude any lingering effects of presurgical SSA treatment on the outcome [49]. However, the evaluation in the study by Shen et al. [26] was made 6 months postoperatively and in the study by Mao et al. [19] 4 months postoperatively. In addition, the preoperative treatment employed in the Mao study was lanreotide LA 30 mg/2 weeks, which has a shorter

half life than octreotide LAR [50]. In the pharmacokinetics study of acromegalic patients by Heron et al. [50], plasma IGF-I levels reached basal levels 1 month after lanreotide 30 mg LA injection. Both intervals (6 months for octreotide LAR and 4 months for lanreotide 30 mg LA) could be considered as a "safe" washout period for SSA effects [49] and [51]. In the study by Fougner et al. [27] a beneficial effect of SSA pre-surgical treatment could not be proved. A key aspect of that study is that definitive treatment, like radiation therapy and repeated surgery were performed postoperatively in 6 patients (radiation 4, surgery 2) in the direct surgery group and 2 patients (radiation 1, surgery 1) in the pre-treated group. These data, complicate the interpretation of long term data, and indirectly point to the possible benefits of pre-treatment. Moreover, the results have a borderline statistical significance ($P = 0.06$), representing a 50% increase in absolute numbers with pre-operative treatment. In our opinion, the long-term data from Fougner et al. [27], with its borderline significance and the potential risk of a type 2 error, and the study by Mao et al. [19], are in line with the combined results of our previous meta-analysis [29]. This opinion is shared with Jacob et al. [52] in their excellent review, in which they suggest that SSA pre-treatment should be considered in patients with GH producing macroadenomas in those centres where overall surgical cure rates for GH-secreting macroadenomas with acromegaly are below 50% [52]. The results of this study should probably not be applied to large reference centres with significant surgical expertise where pre-treatment results are probably less efficacious [29]. However, it is important to consider that in real clinical practice this is not the case, as most pituitary surgery is performed by less experienced surgeons even in developed countries [53].

In conclusion, we posit that in centres without optimal surgical results, preoperative treatment with SSA of GH-secreting pituitary macroadenomas is 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.

Conflict of interest

Disclosure: LMF, SPD, LPB, SSA, EOB, FPG and SPF have nothing to declare. FC has received honoraria for speaking from Novartis and Pfizer, and unrestricted research grants from Ipsen. No one was related with this article. None of the authors are affiliated to any commercial company.

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