Preoperative octreotide treatment of acromegaly: long-term results of a randomised controlled trial

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Abstract

Objective: Randomised studies have demonstrated a beneficial effect of pre-surgical treatment with somatostatin analogues (SSA) in acromegaly when evaluated early postoperatively. The objective of this study was to evaluate the long-term surgical cure rates.

Methods: Newly diagnosed patients were randomised to direct surgery ($n=30$) or 6-month pretreatment with octreotide LAR ($n=32$). The patients were evaluated 1 and 5 years postoperatively. Cure was defined as normal IGF1 levels and by normal IGF1 level combined with nadir GH <2 mU/l in an oral glucose tolerance test, all without additional post-operative treatment. A meta-analysis using the other published randomised study with long-term analyses on preoperative SSA treatment was performed.

Results: The proportion of patients receiving post-operative acromegaly treatment was equal in the two groups. When using the combined criteria for cure, 10/26 (38%) macroadenomas were cured in the pretreatment group compared with 6/25 (24%) in the direct surgery group 1 year postoperatively ($P=0.27$), and 9/22 (41%) vs 6/22 (27%) macroadenomas, respectively, 5 years postoperatively ($P=0.34$). In the meta-analysis, 16/45 (36%) macroadenomas were cured using combined criteria in the pretreatment group vs 8/45 (18%) in the direct surgery group after 6–12 months ($P=0.06$), and 15/41 (37%) vs 8/42 (19%), respectively, in the long-term ($P=0.08$).

Conclusion: This study does not prove a beneficial effect of SSA pre-surgical treatment, but in the meta-analysis a trend towards significance can be claimed. A potential favourable, clinically relevant response cannot be excluded.

European Journal of
Endocrinology
(2014) 171, 229–235

Introduction

Acromegaly causes a variety of different clinical symptoms and signs, reflecting the increased morbidity for these patients. In addition, active acromegaly is associated with increased mortality, correlated with elevated growth hormone (GH) (1) and insulin-like growth factor 1 (IGF1) levels (2, 3). Therefore, effective treatment of acromegaly is important.

Transsphenoidal pituitary surgery to remove the somatotroph adenoma is considered to be the primary treatment for acromegaly. Despite reports from particularly experienced surgical departments of an overall cure rate as high as 70% (1), reports from national or regional surveys show markedly lower cure rates of 30–40% (4, 5, 6). As expected, the cure rate is

lower in macroadenomas and particularly in invasive adenomas (1).

Medical treatment of somatotroph adenomas with somatostatin analogues (SSA) causes a decline in hormone levels in the majority of patients, although with large individual differences. Moreover, $\sim 2/3$ of naïve patients experience significant tumour shrinkage during treatment with the traditional SSAs (7, 8, 9, 10). These effects were the rationale behind the first studies of preoperative treatment with an SSA. A normalisation of GH and IGF1 could lead to decreased anaesthetical complication rate and lower surgical risk, and both softening and shrinkage of tumour to a less invasive adenoma could facilitate tumour removal (11, 12, 13). We reported the first randomised, controlled study of preoperative octreotide treatment of acromegaly (the POTA study) in 2008, concluding with a better cure rate at the 3 months post-operative evaluation for patients with macroadenomas who had received 6 months pre-surgical treatment with the SSA octreotide (10, 14). Subsequently, three trials have reported similar results (15, 16, 17). However, at present three of these altogether four studies have reported cure at 3–4 months post-operatively only, and the fourth one (17) demonstrates no significant difference in cure rate in the long-term.

The primary endpoint of the POTA study was cure at 3 months postoperatively. We showed a significant effect of pretreatment for macroadenomas but not for microadenomas, albeit with very few patients in the latter group. According to the study protocol, the patients were followed and evaluated annually until 5 years after surgery. Long-term observational data in these patients are of importance, also because a concern has been raised of a potential lingering effect of preoperative SSA at the very early post-operative evaluation resulting in potential false positive results (18, 19).

In this study, we present the results of the post-operative evaluations 1 and 5 years after surgery from the POTA study. There were a small but not negligible number of patients who were lost to follow-up before the final evaluation. To try to avoid a type 2 statistical error, we also performed a meta-analysis on our data for macroadenomas combined with the results of the previously published randomised controlled study with long-term data (17).

Patients and methods

Patients

In the period between September 1999 and October 2004, all newly diagnosed patients with acromegaly in Norway

were considered for inclusion in the POTA study. All five university hospitals treating acromegaly in Norway participated in the study. Of all 83 patients, 62 (75%) were included in the study, as previously described in detail (10).

A written informed consent was obtained from each patient. The study was approved by the Regional Committee for Medical and Health Research Ethics and The Norwegian Medicines Agency, and was conducted according to the Declaration of Helsinki II. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00521300) identifier: NCT00521300.

Study design and treatment

After a baseline evaluation, the included patients were randomised to either direct transsphenoidal surgery (direct surgery group, $n=30$) or to 6 months' treatment with octreotide before surgery (pretreatment group, $n=32$). The randomisation was carried out separately for each study centre in blocks of four, but with a central allocation with sealed envelopes.

The patients randomised to pre-surgical octreotide treatment received s.c. octreotide 50 μg t.i.d. the first week and then 100 μg t.i.d. the second week. From the third week, the patients received octreotide LAR 20 mg i.m. every 28th day until surgery after ~ 6 months. All patients in the pretreatment group underwent surgery with therapeutic levels of octreotide. The clinical effects of octreotide pretreatment have been described previously (10).

All patients were evaluated 3 months postoperatively (14). After this evaluation, the patients could receive additional treatment (medical, re-surgery or radiation) if considered necessary by the endocrinologist at each study centre. No guidelines for the treatment 3 months postoperatively and onwards were stated in the protocol. According to the protocol, the patients were then evaluated at 1 year and annually until 5 years after the initial surgery. One of the patients with microadenoma in the pretreatment group was not operated due to the patient's request based on excellent biochemical and tumour response, and was excluded from the present analyses. Two patients died before the 5-year evaluation, and available data were insufficient for any classification of cure at 5-year post-operative evaluation in an additional three patients, all having macroadenomas. For three patients, no hormone data were available 5 years post-operatively, but since they had received additional post-operative treatment they could be classified as not cured. In total, classification of cure status at 5 years postoperatively was available in 56 patients (46 macroadenomas).

Investigations

A central retrospective evaluation of the magnetic resonance imaging scan at inclusion classified each tumour as a macroadenoma (largest diameter ≥ 10 mm) or a microadenoma (10).

Fasting serum samples were drawn to analyse IGF1 levels locally, both at 1 and 5 years following initial surgery. At 1 year postoperatively, additional serum was stored at -70°C , and IGF1 level was later measured centrally in one run using an ELISA Kit (R&D Systems, Minneapolis, MN, USA), as described previously (14). In five patients, frozen serum was missing, and the locally measured IGF1 level with the local reference value was used instead. At 5-year post-operative evaluation, serum IGF1 level was measured consecutively by routine methods at each local hospital laboratory. However, except for the two earliest analyses from one of the laboratories where IGF1 levels were measured by a kit from Nichols Institute (Nijmegen, the Netherlands), all laboratories ($n=4$) used Siemens Immulite (Erlangen, Germany).

An oral glucose tolerance test (OGTT) was performed in all patients 1 year postoperatively, and in 46 patients 5 years postoperatively. GH measurements were performed consecutively at the local hospital laboratories.

Meta-analysis

Shen *et al.* (17) present 6 months' follow-up results and long-term results after a mean of 26.6–28.8 months. In this study, 11 patients received gamma-knife therapy about 6 months postoperatively. These patients were all classified as non-cured at the subsequent evaluations (personal communication, Prof. Zhao). We performed one meta-analysis on these 6-months follow-up results combined with our 1-year post-operative results, and another meta-analysis on the last follow-up data from Shen *et al.* combined with our 5-year post-operative data.

Table 1 Additional treatment for acromegaly until 1 year postoperatively.

	Preoperative SMS ($n=31$)	Direct surgery ($n=30$)
Medical therapy (n)	8	5
SMS	6	3
Pegvisomant	1	1
SMS+cabergoline	1	1
Radiation therapy (n)	1	4
Repeated surgery (n)	1	2
Total (n)	8	9

Definition of cure

A patient was considered cured when IGF1 level was equal to or below upper limit of normal (ULN) and GH nadir was ≤ 2 mU/l during an 75 g OGTT, without having received any treatment for acromegaly after the initial surgery. Results are also presented for cure defined only by IGF1 level equal to or lower than ULN.

Statistical analyses

The statistical analyses were performed using SPSS Statistics, version 20.0 (IBM Corp.), except for the meta-analysis and forest plots, which were performed using Review Manager 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark). The χ^2 test was used for categorical variables except for analyses within the microadenoma group where Fisher's exact test was used. P values <0.05 were considered significant. No adjustment was made for multiple testing.

Results

Post-operative acromegaly treatment

Before the 1-year post-operative evaluation, 17 patients had received additional, post-operative treatment for acromegaly. Of these, eight patients were in the pretreatment group and nine in the direct surgery group (8/31 vs 9/30; $P=0.72$). Details regarding the additional treatment are given in Table 1.

At the 5-year post-operative evaluation, 30/59 patients had received additional treatment, 15 in each treatment group.

Cure at 1 year postoperatively

For cure defined by an IGF1 level $\leq$ ULN, 12/31 (39%) patients in the pretreatment group and 11/30 (37%) patients in the direct surgery group were cured without post-operative treatment, $P=0.87$. For macroadenomas, 12/26 (46%) patients in the pretreatment group vs 8/25 (32%) patients in the direct surgery group were cured, $P=0.30$. The number of microadenomas was low; details are given in Table 2.

For cure defined by the combined criteria of IGF1 $\leq$ ULN and a nadir GH during OGTT ≤ 2 mU/l, the cure rate was lower. In the pretreatment group, 10/31 (32%) were cured compared with 8/30 (27%) in the direct surgery group, $P=0.63$. Among the macroadenomas,

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Table 2 Cure at 1 year defined by $\text{IGF1} \leq \text{ULN}$ and nadir $\text{GH} \leq 2 \text{ mU/l}$ during OGTT at one year post-operative, without having received any post-operative treatment for acromegaly. Fisher's exact test two-sided used for microadenomas, Pearson Chi-Square used for macroadenomas and total group.

Treatment group	According to IGF1					According to IGF1 and GH				
	No.	Cured	Not cured	Cure %	P value	No.	Cured	Not cured	Cure %	P value
All										
Pretreatment	31	12	19	39	0.87	31	10	21	32	0.63
Direct surgery	30	11	19	37		30	8	22	27	
Microadenomas										
Pretreatment	5	0	5	0	0.17	5	0	5	0	0.44
Direct surgery	5	3	2	60		5	2	3	40	
Macroadenomas										
Pretreatment	26	12	14	46	0.30	26	10	16	38	0.27
Direct surgery	25	8	17	32		25	6	19	24	

10/26 (38%) in the pretreatment group and 6/25 (24%) in the direct surgery group were cured, $P=0.27$. Details for the microadenomas are given in Table 2.

Cure at 5 years postoperatively

Cure defined as $\text{IGF1 level} \leq \text{ULN}$ was achieved without any additional post-operative treatment in 12/28 (43%) patients in the pretreatment group and 11/28 (39%) in the direct surgery group, $P=0.79$. For macroadenomas, 10/23 (43%) were cured in the pretreatment group vs 8/23 (35%) in the direct surgery group, $P=0.55$. Details are given in Table 3.

For cure defined by both IGF1 and nadir GH levels, 11/27 patients (41%) were cured in the pretreatment group and 8/26 (31%) in the direct surgery group, $P=0.45$. Among patients with macroadenomas, 9/22 (41%) patients were cured in the pretreatment group vs 6/22 patients (27%) in the direct surgery group, $P=0.34$. For microadenomas, see Table 3.

Meta-analysis

When pooling our results from the 1 year post-operative evaluation with 6 months' post-operative data from Shen *et al.* (17) and using only IGF1 as cure criterion, the number of cured macroadenomas after pretreatment was 20/45 (44%) for the pretreatment group vs 12/45 (27%) for the direct surgery group, $P=0.08$. The meta-analysis is visualised in a forest plot, Fig. 1A.

Accordingly, for cure defined by the combined IGF1 and GH criterion, 16/45 (36%) patients with macroadenomas were cured in the pretreatment group vs 8/45 (18%) in the direct surgery group, $P=0.06$, Fig. 1B.

When our 5-year post-operative data on macroadenomas were pooled with data from the last follow-up in the study by Shen *et al.*, and using only IGF1 as criterion for cure, the number of cured macroadenomas was 17/42 (40%) in the pretreatment group and 12/43 (28%) in the direct surgery group, $P=0.23$, Fig. 1C. Using the combined cure criteria, 15/41 (37%) patients with macroadenomas

Table 3 Cure at 5 year defined by $\text{IGF1} \leq \text{ULN}$ and nadir $\text{GH} \leq 2 \text{ mU/l}$ during OGTT at five years post-operative, without having received post-operative treatment for acromegaly. Fisher's exact test two-sided used for microadenomas, Pearson Chi-Square used for macroadenomas and total group.

Treatment group	According to IGF1					According to IGF1 and GH				
	No.	Cured	Not cured	Cure %	P value	No.	Cured	Not cured	Cure %	P value
All										
Pretreatment	28	12	16	43	0.79	27	11	16	41	0.45
Direct surgery	28	11	17	39		26	8	18	31	
Microadenomas										
Pretreatment	5	2	3	40	1.0	5	2	3	40	1.0
Direct surgery	5	3	2	60		4	2	2	50	
Macroadenomas										
Pretreatment	23	10	13	43	0.55	22	9	13	41	0.34
Direct surgery	23	8	15	34		22	6	16	27

Figure 1

Meta-analyses. A and B, Meta-analyses of cure at 6–12 months post-operative evaluation; A, Cure defined by $IGF1 \leq ULN$; B, Cure defined by $IGF1 \leq ULN$ and nadir GH during OGTT ≤ 2 mU/L; C and D, Meta-analyses of cure at long-term post-operative evaluation, 5 years (present study) and last follow-up (17). C, Cure defined by $IGF1 \leq ULN$. D, Cure defined by $IGF1 \leq ULN$ and nadir GH during OGTT ≤ 2 mU/L. Full colour version of this figure available via <http://dx.doi.org/10.1530/EJE-14-0249>.

were cured in the pretreatment group vs 8/42 (19%) in the direct surgery group, $P = 0.08$, Fig. 1D.

Discussion

This randomised study of preoperative SSA treatment in acromegaly is the second study to present randomised long-term cure data. No significant impact of preoperative

treatment of macroadenomas is found at 1 and 5 years postoperatively, despite the previously published benefit for macroadenomas at the 3-month post-operative evaluation. However, when pooling the data with the other long-term study, a trend towards benefit of pretreatment can be claimed. For macroadenomas, twice as many patients were cured without additional treatment 6–12 months after the initial surgery in the pretreatment

group (36%) vs the direct surgery group (18%). The results in our study were less discriminate, but with the same tendency as in the Chinese study. A possible explanation is that Shen *et al.* only included invasive macroadenomas and demonstrate a correlation of cure to shrinkage to a less invasive adenoma during pretreatment. Another possible bias of the meta-analysis is that the studies were heterogeneous with respect to the duration of octreotide treatment preoperatively, and that the 6-month post-operative evaluation in Shen *et al.*'s study may not be entirely comparable with the 12-month evaluation in our study. Nevertheless, data are available for only 90 patients altogether, with a potential risk of a type 2 statistical error. The 5-year post-operative results are also comparable, representing a 50% increase in absolute numbers, but not statistically significant. When presenting the data combined with the long-term results reported by Shen *et al.* (17), the result is very similar to the meta-analysis 6–12 months postoperatively, with a trend for increased cure of macroadenomas by pretreatment representing a doubled cure rate in the pretreated group.

Particularly octreotide but also lanreotide has been proven to have a long biological half-life when given in slow-release formulas, and can be detected in circulation many weeks after injection (20, 21). A phase I study demonstrated that the concentration of octreotide LAR decreases slowly to immeasurable values in the first 11 weeks after a single injection (22). A clinical study of SSA withdrawal has demonstrated suppressed hormone levels for several months in some patients (23). A potential hangover effect of SSA at the 3–4 months' post-operative evaluation causing false results is therefore possible, necessitating analysis of long-term cure data. This POTA study was planned with yearly assessments from 1 to 5 years postoperatively, and all patients underwent the first year post-operative control.

Owing to lack of cure after the initial surgery, several patients received post-operative additional treatment. The proportion of patients receiving adjuvant treatment was equal in both groups. However, the study protocol did not standardise the indication for, or the selection of, adjuvant therapy. Within the first year both gamma-knife therapy and medical treatment were given, as well as renewed surgery in a few patients. Medical treatment was chosen in all pretreated patients (8/8), compared with 5/9 patients in the direct surgery group. Nevertheless, all patients receiving additional treatment were considered as not cured despite hormone levels and this would therefore does not affect the cure rate in the long-term. However, it is the hormone status in the long term that is clinically

relevant and important for each patient. Among the 40 patients considered as not cured after IGF1 3 months post-operatively (14), less than half of the patients received additional acromegaly treatment at 1 year postoperatively. This demonstrates undertreatment in several patients, but can probably also reflect a discrepancy between the locally measured IGF1 level and the central measurement performed both at 3 and 12 months postoperatively. This discrepancy may also explain the lower proportion of cured patients at 1 year compared with 5-year postoperatively, when only locally measured IGF1 levels were available.

In this study, all patients with newly diagnosed acromegaly were considered for inclusion. Therefore, in contrast to the other published studies on preoperative SSA treatment, also microadenomas were included. The proportion of microadenomas was low, but fortunately, the randomisation ensured five patients with microadenomas in each treatment group. As discussed in our first paper (14), a possible unfavourable effect of pretreatment could be suspected when considering cure rate at 3 and 12 months following surgery since none of the direct surgery microadenomas were cured. However, at 5-year post-operative evaluation the results were equal in the two groups. Anyway, the groups were too small to draw any conclusions, and additional studies are warranted.

In conclusion, this randomised study of preoperative treatment with SSA in acromegaly did not provide statistical documentation for a beneficial long-term effect. In meta-analyses of a total of 90 and 83 patients evaluated at 6–12 months and later, respectively, approximately twice as many patients were cured among the pretreated patients compared with the direct surgery group. However, there were not significant differences between the cure rates. Therefore, more long-term response studies are required. If future studies show effects comparable to the present results, this would be very important as a doubled surgical cure rate would be a major improvement in the treatment of acromegaly.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. S L Fougner and S M Carlsen have received lecture fees/travel grants from Ipsen Norway and Novartis Norway.

Funding

This study was carried out by the POTA study group which is a subgroup of the 'Norwegian Neuroendocrine Interest group' (NNI). The annual

meetings of NNI, where all authors have participated, are supported by Novartis Norway. The study was also directly supported by Novartis Norway who paid the salary for a part-time study nurse (20% position), supported the drug used (Sandostatin and Sandostatin LAR) free of charge and carried the expenses when the study nurse checked the raw data at each study site.

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Received 28 March 2014

Revised version received 22 May 2014

Accepted 27 May 2014