CLINICAL STUDY

Preoperative lanreotide treatment in acromegalic patients with macroadenomas increases short-term postoperative cure rates: a prospective, randomised trial

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Abstract

Objective: To investigate whether 4-month preoperative lanreotide treatment would improve the surgical cure rate of newly diagnosed acromegalic patients with macroadenomas.

Design: A prospective, randomised study.

Methods: After a baseline evaluation, patients were randomly assigned to 4-month preoperative treatment with lanreotide (starting with 30 mg/2 weeks i.m. and increasing to 30 mg/week i.m. at week 8 if mean GH > 2.5 µg/l on GH day curves; pretreatment group, Group 1) or to transsphenoidal surgery (direct surgery group, Group 2). Cure was evaluated 4 months postoperatively primarily by fasting IGF1 less than or equal to age-adjusted upper limit of normal.

Results: A pool of 108 patients was randomly divided into two groups. Five patients in each group were lost to follow-up during the study period, so 49 patients in each group were analysed. At baseline, no difference was observed between the two groups. Cure was established in 24 of 49 (49.0%, 95% confidence interval (CI), 35.0–63.0%) pretreated patients (Group 1) versus 9 of 49 (18.4%, 95% CI, 7.6–29.2%) direct surgery patients (Group 2; $P=0.001$). Surgical morbidity was recorded in 12 patients (12.2%) and was similar in Group 1 and 2 patients (14.3 and 10.2% respectively; $P=0.538$). The postoperative hospital stay was similar between groups: being 4.5 ± 1.6 days in Group 1 vs 4.8 ± 1.9 days in Group 2 ($P=0.328$).

Conclusions: Pretreatment with lanreotide before transsphenoidal surgery improves surgical cure rates in patients with GH-secreting pituitary macroadenomas. Pretreatment does not affect surgical complications or duration of hospital stay (ClinicalTrials.gov number, NCT00993356).

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Introduction

Acromegaly is a rare disease caused by a GH-secreting adenoma or (rarely, about 1%) by excessive GH-releasing hormone secretion, usually by a carcinoid tumour of the lung or gastrointestinal tract (1). The incidence of acromegaly is about 3–4 per million per year and the prevalence is 60–70 per million, and there are no geographical or sex differences (2). Clinical features of acromegaly include acral enlargement, prognathism, jaw malocclusion, arthropathy, carpal tunnel syndrome, hyperhydrosis, sleep apnoea and visceromegaly (3, 4).

Transsphenoidal neurosurgery, which allows selective removal of pituitary adenomas, is the current first treatment for acromegaly in the majority of patients. Its effects on GH and insulin-like growth factor 1 (IGF1) secretion are rapid, and the operations have low

morbidity and very low mortality (5, 6). However, surgery for macroadenomas causing acromegaly has a much lower success rate than that for microadenomas. In experienced hands, microadenomas can be cured around 90% of the time, whereas with macroadenomas the figure is around 50% (7). This is particularly true with tumours that extend into the cavernous sinus, where surgical success is < 50% (8). Medical treatment of acromegaly with somatostatin analogues (SSAs) can lead to normalised GH and IGF1 levels in up to 60% of cases (9) and relief of symptoms (3). Lanreotide is a synthetic SSA, a naturally occurring inhibitory hormone which blocks the release of several other hormones, including GH, thyrotrophin, insulin and glucagon. SSA treatment may cause shrinkage of GH-secreting pituitary adenomas (9, 10). Theoretically, this could improve the likelihood of a radical resection,

particularly in macroadenomas. Furthermore, it has been suggested that SSA treatment softens the tumour parenchyma and thereby facilitates tumour removal (11). Finally, it has been reported that SSA pretreatment leads to a shortening of postoperative hospital stay (12).

Previous studies addressing preoperative SSA treatment and subsequent surgical cure rates are conflicting, reporting a benefit (12, 13) or no difference with SSA treatment (11, 14, 15). Since most reported studies were rather small and were made in retrospect, we conducted a prospective, randomised study to investigate whether 4-month preoperative lanreotide treatment would improve the surgical cure rate of newly diagnosed acromegalic patients with macroadenomas. We also aimed to investigate whether there were differences in the incidence of surgical complications and duration of neurosurgical hospital stay.

Patients and methods

Patient selection

From January 1, 2004 to December 30, 2007, patients with newly diagnosed active acromegaly due to GH-secreting macroadenomas were considered eligible for the study. A pituitary macroadenoma was more than 10 mm in size. The inclusion criteria were as follows: newly diagnosed, previously untreated patients with a GH nadir more than $2.5 \mu\text{g/l}$ during a standard 75-g, 2-h oral glucose tolerance test (OGTT); IGF1 levels at least 1.3 times the upper limit of the age-adjusted normal range (ULN); pituitary macroadenomas verified by a pituitary magnetic resonance imaging (MRI) scan; and age between 18 and 80 years. The exclusion criteria were as follows: immediate surgery indicated by clinical criteria, pregnancy, contraindications on MRI scan, and patients judged not suitable to participate in the study for other reasons such as personality disorders and

alcohol abuse. In this study, the patients weren't selected based on response to a somatostatin test. A power calculation verified that 48 patients in each group would be necessary to detect an increase in cure rate from 15% (9) to 40% with an α error level of 5% and a β error level of 80%. Allowing for a follow-up loss rate of 10%, the enrolment was closed when 108 patients were included, and 54 patients were allocated to each group.

The trial was performed in the Department of Neurosurgery, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, People's Republic of China. The study was previously approved by the Institutional Review Board of the First Affiliated Hospital, Sun Yat-sen University. Written informed consent was obtained from each patient before randomisation. The study is registered at ClinicalTrials.gov (NCT00993356).

Treatment plan

After a baseline evaluation, patients were randomised to 4-month preoperative treatment with lanreotide (Somatuline LA, Ipsen, Paris, France; pretreatment group, Group 1) or to transsphenoidal surgery (direct surgery group, Group 2). Group 1 patients received lanreotide for 16 weeks before the surgical resection (starting with 30 mg/2 weeks i.m. and increasing to 30 mg/week i.m. at week 8 if mean GH $> 2.5 \mu\text{g/l}$ on the GH day curve (GHDC); GHDC: 9×30 -min samples collected in the morning after an overnight fast via an indwelling catheter inserted in an arm vein and while the patient was resting).

In both groups, surgical resection (transsphenoidal adenomatectomy) was performed by two neurosurgeons dedicated to the treatment of pituitary tumours (Z M and H W). The surgical results were assessed 16 weeks following surgery, and mean GH $> 2.5 \mu\text{g/l}$ in a GHDC was subsequently started on lanreotide (starting with 30 mg/2 weeks i.m. and increasing to 30 mg/week i.m. at 8 weeks later if mean GH $> 2.5 \mu\text{g/l}$; Fig. 1).

Figure 1 Study protocol. D, day; W, week.

Imaging assessments

Tumour size was estimated from MRI studies performed prior to study entry, after lanreotide treatment but prior to surgery (Time 1) and after surgery (Time 2). The MRI scans consisted of T1W spin echo sequences (e.g., TR: 500–600 ms, TE: 15 ms) in coronal and sagittal planes constructed as contiguous slices 3 mm thick or less and performed at 1.5 T. All assessments were performed by a single neuroradiologist, and scans were presented for evaluation without clinical details. Tumour volumes were calculated according to the formula volume = height × length × width × $\pi/6$ (Ref. (16)). Maximum tumour dimensions were measured in sagittal (vertical height and anterior–posterior length) and coronal (width) views.

Assays

Serum GH levels were measured by a two-site chemiluminescent immunometric assay (Immulite/Immulite 1000 GH (hGH) kit, EURO/DPC Ltd, Gwynedd, UK, intra-assay coefficient of variation (CV): 5.3–6.5%, interassay CV: 5.7–6.2%, calibration range: up to 40 ng/ml (52 µg/l), sensitivity: up to 0.01 ng/ml (0.013 µg/l)). Serum IGF1 levels were measured by a two-site immunoenzymometric assay (OCTEIA IGF1 kit, Immunodiagnostic Systems Ltd, Boldon, UK, expected values depending on age (20–30 years: 11.7–36.1 nmol/l; 30–40 years: 2.9–25.8 nmol/l; 40–50 years: 6.4–19.3 nmol/l; 50–60 years: 4.6–27.5 nmol/l; 60–70 years: 3.9–25.7 nmol/l; >70 years: 6.6–25.0 nmol/l; intra-assay CV: 2.3–3.5%; interassay CV: 7.0–7.1%; sensitivity: 0.25 nmol/l)).

Statistical analysis

The aim of the study was to investigate whether 4-month treatment with lanreotide before transsphenoidal surgery in newly diagnosed acromegalic patients with macroadenomas would improve the outcome, using cure rate at a 4-month postoperative evaluation as the primary end point. Cure was evaluated 4 months postoperatively primarily by fasting IGF1 less than or equal to age-adjusted ULN. Secondary end points included postoperative hospital stay duration and complication rates. Quantitative data are presented as means ± s.d., and qualitative data are presented as percentages. Comparisons among groups were performed using Student's *t*-test for quantitative data and the Pearson's χ^2 test for qualitative variables. Statistical analysis was performed using the Statistical Program/SPSS for Windows, version 11.5 (Chicago, IL, USA). A *P* value (two-tailed) of <0.05 was considered statistically significant.

Results

Baseline patient characteristics

Of the 128 acromegalic patients with macroadenomas, 112 fulfilled the inclusion criteria and were recruited for the trial; four refused to participate. Two groups of 54 patients each were obtained from a randomisation of 108 patients. Five patients of each group were lost to follow-up during the study period; therefore, 49 patients of each group were analysed in this study. At baseline, no difference was observed between the two groups in gender, patient age, GH nadir during OGTT, IGF1, type of macroadenoma or tumour volume, nor in the rates of hypertension, electrocardiogram abnormalities, left ventricular hypertrophy, ventricular or supraventricular tachycardia, or sleep apnoea (Table 1).

Effect of lanreotide treatment on surgical outcome

Cure, as defined by IGF1 less than or equal to the ULN 4 months postoperatively, was established in 24 of 49 (49.0%, 95% confidence interval (CI), 35.0–63.0%) pretreated patients (Group 1) versus 9 of 49 (18.4%, 95% CI, 7.6–29.2%) direct surgery patients (Group 2; *P*=0.001). Cure was also estimated using age-adjusted

Table 1 Baseline data according to treatment group.

Characteristic	Group 1 (n=49), n (%)	Group 2 (n=49), n (%)	<i>P</i>
Gender			0.536
Male	31 (63.3)	28 (57.1)	
Female	18 (36.7)	21 (42.9)	
Age (years) ^a	48.5 ± 12.4	43.8 ± 14.1	0.436
GH nadir during OGTT (µg/l) ^a	20.4 ± 15.7	18.9 ± 16.3	0.247
Mean (range)	21.5 (3.2–48.5)	19.8 (2.9–45.7)	
IGF1 (nmol/l) ^a	87.9 ± 25.1	96.1 ± 23.7	0.083
Type of macroadenoma			0.758
Intrasellar	15 (30.6)	12 (24.5)	
Suprasellar	25 (51.0)	26 (53.1)	
Invasive	9 (18.4)	11 (22.4)	
Tumour volume (cm ³) ^a	14.1 ± 8.2	12.5 ± 7.9	0.069
Hypertension			0.678
Yes	18 (36.7)	20 (40.8)	
No	31 (63.3)	29 (59.2)	
ECG abnormalities			0.686
Yes	27 (55.1)	25 (51.0)	
No	22 (44.9)	24 (49.0)	
Left ventricular hypertrophy			0.585
Yes	9 (18.4)	7 (14.3)	
No	40 (81.6)	42 (85.7)	
Ventricular or supraventricular tachycardia			0.564
Yes	8 (16.3)	6 (12.2)	
No	41 (83.7)	43 (87.8)	
Sleep apnoea			0.538
Yes	7 (14.3)	5 (10.2)	
No	42 (85.7)	44 (89.8)	

OGTT, oral glucose tolerance test; ECG, electrocardiogram.

^aValues given as means ± s.d.

cut-off levels of IGF1 ranging from 80 to 120% of the ULN (Table 2). Pretreatment significantly increased cure rates as evaluated by IGF1 at cut-off levels ranging from 90 to 120% of the ULN ($P=0.025- <0.001$). Only 1 of the 11 patients with signs of cavernous sinus invasion in the direct surgery group (Group 2) was cured. However, 4 of 9 patients with signs of cavernous sinus invasion after pretreatment with lanreotide were cured (Group 1). When adding a GH nadir during an OGTT $\leq 1.0 \mu\text{g/l}$ to the cure criteria, five patients lost their status of being cured. Thus, the overall cure rate was reduced to 38.8% (Group 1) and 18.4% (Group 2) respectively ($P=0.025$).

Effect of lanreotide treatment on tumour volume

In the pretreated patients (Group 1), all had reduction of their adenoma size after 4-month lanreotide treatment (median percentage was 34.8% (range 7.5–62.5)). Among those with tumour volume reduction, 42 (85.7%) showed shrinkage $>20\%$ (Fig. 2). Initial tumour volume (13.5 ± 7.8 vs $14.6 \pm 8.5 \text{ cm}^3$; $P=0.218$) was equally distributed among cured and non-cured patients. However, there was a difference in tumour volume change during pretreatment (-45 ± 18 vs $-21 \pm 15\%$; $P=0.003$) between the cured and non-cured patients.

Complications of surgery

No operative or perioperative deaths occurred. Surgical morbidity was recorded in 12 patients (12.2%) and was similar in Group 1 and 2 patients (14.3 and 10.2% respectively; $P=0.538$). Most complications were mild and caused no permanent disability. The most frequent

complication was hyponatraemia (defined as 130 mmol/l serum sodium concentration), which occurred in four patients (three in Group 1 and one in Group 2), and was responsive to simple water restriction alone in all patients. Difficult intubation requiring postponement of the surgery for one day and a subsequent one-day stay in the intensive care unit were encountered in three patients (one in Group 1 and two in Group 2). Two patients (one in each group) experienced hypoxaemia during anaesthesia without clinical consequences. Two patients (one in each group) experienced transient liquorrhoea, and one patient in Group 2 experienced sinusitis. The postoperative hospital stay was similar between the groups, being 4.5 ± 1.6 days in Group 1 versus Group 2 ($P=0.328$).

Discussion

Postoperative remission rates of GH-secreting pituitary adenomas are expected to correlate negatively with the preoperative baseline GH (and probably IGF1) value, the volume of the tumour (especially when exhibiting infiltrative growth) and the consistency of the adenoma. Considering the ability of SSAs to lower GH and IGF1 concentrations, to shrink GH-secreting adenomas, and to possibly soften their consistency, it was thought that SSA pretreatment might improve the results of surgery in acromegaly (15). However, the effect of prior SSA treatment on operative outcome in acromegaly has been controversial. No beneficial effect (11, 14, 15, 17) and improvement of surgical results (12, 13, 18–20) have both been reported. Inclusion of patients with a microadenoma and of patients who had previously received medical, surgical or irradiation treatment, lack of matching for invasiveness or IGF1 concentration, reliance on single GH values rather than on day

Table 2 Cure rate according to insulin-like growth factor 1 (IGF1) less than or equal to upper limit of normal (ULN) 4 months postoperatively.

IGF1 as percentage of ULN (%)	Treatment group	Cured	Not cured	P	Cure rate (95% CI)
80	Group 1	7	42	0.538	14.3% (4.5–24.1%)
	Group 2	5	44		10.2% (1.7–18.7%)
85	Group 1	10	39	0.424	20.4% (9.1–31.7%)
	Group 2	7	42		14.3% (4.5–24.1%)
90	Group 1	19	30	0.025	38.8% (25.2–52.4%)
	Group 2	9	40		18.4% (7.6–29.2%)
95	Group 1	21	28	0.009	42.9% (29.0–56.8%)
	Group 2	9	40		18.4% (7.6–29.2%)
100	Group 1	24	25	0.001	49.0% (35.0–63.0%)
	Group 2	9	40		18.4% (7.6–29.2%)
105	Group 1	26	23	0.001	53.1% (39.1–67.1%)
	Group 2	10	39		20.4% (9.1–31.7%)
110	Group 1	28	21	<0.001	57.1% (43.2–71.0%)
	Group 2	10	39		20.4% (9.1–31.7%)
115	Group 1	29	20	<0.001	59.2% (45.4–73.0%)
	Group 2	11	38		22.4% (10.7–34.1%)
120	Group 1	31	18	<0.001	63.3% (49.8–76.8%)
	Group 2	11	38		22.4% (10.7–34.1%)

CI, confidence interval.

Figure 2 Representative MRI images demonstrating shrinkage of a macroadenoma. The three frames show coronal images at baseline (A) and after 16 weeks of lanreotide therapy (residual volume, 49.4%; B) and 16 weeks after surgical resection (residual volume, 7.6%; C). The patient was cured.

profiles, variable SSA doses and treatment times, as well as liberal criteria for cure (11–15, 17–20) are all factors that make it difficult to definitively prove or disprove a positive effect. The current study was

designed to avoid these shortcomings. Cure rates are close to 90% in experienced centres for patients with microadenomas (21, 22); such patients were therefore excluded. The lanreotide dose and treatment time were standardised.

This prospective randomised study indicates that preoperative lanreotide treatment of newly diagnosed acromegalic patients before transsphenoidal surgery leads to an increased surgical cure rate in patients with macroadenomas. The cure rates that we observed were 18.4% in newly diagnosed acromegalic patients with macroadenomas treated directly with transsphenoidal surgery and 49.0% in patients pretreated for 6 months with lanreotide and remaining on treatment during the surgical procedure ($P=0.001$). These findings compare favourably with a previous study in which the cure rate was 16% in direct surgery patients versus 50% in octreotide-pretreated patients (20). However, in a single-centre study like this, overall cure rates were expected to be higher than the results obtained from a multicentre study like that by Carlsen *et al.* (20). Secondly, in the present study, cure evaluation was performed at least 16 weeks postoperatively, whereas in the study by Carlsen *et al.* it was only 12 weeks after the operation (20). Our evaluation time fits the present guidelines, which demand at least a 4-month delay in evaluation when using a long-acting SSA (10). This is thought to prevent a 'hangover' effect of preoperative SSA treatment skewing the postoperative evaluation. Several studies have shown that achieving normal IGF1 levels is a good prognostic factor for acromegaly in terms of morbidity (23–25) and mortality (26, 27). There is general agreement that achieving GH levels $\leq 2.5 \mu\text{g/l}$ is not sufficient for the disease to be considered controlled; it is thought that the persistence of a continuous, albeit minor, hypersecretion of GH (which can be detected with very sensitive assays) may promote the increased IGF1 levels seen in some patients (28). The situation in which patients have normal IGF1 levels but high GH levels occurs less frequently (29). Thus, in the current study, the criterion that we applied for cure rate was IGF1 less than or equal to age-adjusted ULN.

In contrast with one previous report (12) but in agreement with another (20), pretreatment with SSA did not affect the duration of hospital stay, nor did we observe any difference in surgical complication rates between the study groups. In conclusion, pretreatment with lanreotide before transsphenoidal surgery improves surgical cure rates in patients with GH-secreting pituitary macroadenomas. Pretreatment does not affect surgical complications or duration of hospital stay.

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.

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