CLINICAL STUDY

A comparison between octreotide-LAR and lanreotide-SR in the chronic treatment of acromegaly

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Abstract

Background: At present long-acting somatostatin analogs represent the first-line medical treatment of acromegaly. These drugs produce stable suppression of GH in most sensitive patients and IGF-I normalization in many; they also increase the compliance of acromegalic patients. The recent availability of octreotide (OC)-LAR, a somatostatin analog to be administered at 28-day intervals, has prompted us to compare, in the same group of patients, its effects and those of another somatostatin analog already available, lanreotide-SR (LSR, to be administered at 14-day intervals).

Patients: Twelve somatostatin analog-sensitive acromegalic patients with active disease were enrolled in a prospective open sequential study after giving their informed consent. After chronic treatment with LSR (6–24 months), the patients were changed to treatment with OC-LAR, without wash-out. LSR had been administered at individually tailored dosages (30 mg i.m. at 7–21-day intervals, median 10 days – every 7 days in seven patients, 10 days in two patients, 14 days in two patients and 21 days in one patient) according to GH and IGF-I responses. Disease stability was obtained, as shown by maximal GH/IGF-I suppression without any significant hormonal change between the last two control measurements. OC-LAR was administered i.m. at 28-day intervals six times at the dosage of 20 mg for the first three times and 10 or 30 mg for the last three times (according to individual GH/IGF-I responses). GH (mean of three, hourly samples) and IGF-I concentrations were evaluated on the same day as each administration of the drug, before its injection.

Results: GH and IGF-I values were significantly decreased by LSR treatment. GH decreased from $41.6 \pm 14.6 \mu\text{g/l}$ (mean $\pm$ s.e.) to $7.2 \pm 1.5 \mu\text{g/l}$ ($P < 0.02$), whereas IGF-I values declined from $959 \pm 95 \mu\text{g/l}$ to $460 \pm 61 \mu\text{g/l}$ ($P < 0.00001$), expressed as absolute values, and from $287 \pm 30\%$ to $137 \pm 19\%$ expressed as percentage of the upper limit of normal range (%ULNR). At the end of the last cycle, OC-LAR treatment achieved a significant further suppression both in GH (to $5.1 \pm 1.1 \mu\text{g/l}$, $P < 0.05$ compared with LSR) and in IGF-I concentrations (to $374 \pm 60 \mu\text{g/l}$, $P < 0.05$ compared with LSR, and to $112 \pm 19\%$ as %ULNR). LSR decreased GH concentrations to less than $2.5 \mu\text{g/l}$ in one patient and normalized IGF-I concentrations in four patients. OC-LAR decreased GH concentrations to less than $2.5 \mu\text{g/l}$ in four patients and normalized or near-normalized IGF-I concentrations (i.e. to $< 110\%$ ULNR) in eight patients.

Conclusions: These preliminary results show that the once-monthly OC-LAR administration schedule proved more efficacious than LSR given every 7–21 days, in a greater number of acromegalic patients.

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Introduction

Long-acting somatostatin analogs at present represent the first-line medical treatment in acromegaly (1). They achieve stable suppression of growth hormone (GH) in most sensitive patients and normalization of insulin-like growth factor (IGF)-I in many; their administration schedule also increases the compliance of acromegalic patients. Although initial trans-sphenoidal surgery still appears to be the best option for many patients with GH-secreting adenomas, somatostatin analogs are now undergoing evaluation as primary treatment in some

selected patients when the possibility of surgical cure is low. Their use as primary treatment is supported by a recent study that showed no significant difference in the percentage of responders and in GH concentrations between patients previously treated by non-curative neurosurgery and then treated by octreotide, and patients whose primary treatment was with octreotide (2).

Among somatostatin analogs, lanreotide-SR (LSR) is widely available and is administered at intervals ranging from 10 to 14 days (3). The recent availability of octreotide-LAR (OC-LAR), a somatostatin analog to be

Table 1 Demographic and clinical data.

Patient no.	Sex	Age (yr)	Tx	Rx	CT/MRI†	Basal GH (μg/l)	Basal IGF-I (μg/l)
1	M	57	—	—	μ	14	879
2	M	47	—	—	N	16.4	1086
3	M	49	+	—	R	46	1216
4	M	28	—	—	M	130	1400
5	F	58	+	+	ES	9	560
6	F	59	—	—	N	9	590
7	F	60	+	+	R	37	783
8	F	71	—	—	μ	23	750
9	F	60	—	—	M	160	1634
10	M	76	—	—	M	40	900
11	F	30	+	—	R	7.7	705
12	M	49	+	—	R	7.7	1000

Tx, previous neurosurgical treatment; Rx, previous radiotherapy; †neuroradiological imaging: μ = microadenoma, M = intrasellar macroadenoma, R = remnant of adenoma, ES = empty sella, N = normal.

administered at 28-day intervals (4, 5), has prompted us to compare the effects of these two long-acting somatostatin analogs on hormonal concentrations, in the same group of acromegalic patients.

Patients and methods

Patients

Twelve acromegalic patients (six women and six men, aged 28–76 years, median 58 years) with active disease (according to their clinical profile: high GH concentrations not suppressible by oral glucose load to less than 1 μg/l, and increased age-matched IGF-I concentrations) were enrolled in a prospective open sequential study. Five had been previously treated by neurosurgery and two had been irradiated 5–20 years before the study began. At neuroradiological pituitary imaging, three had macroadenoma, two had microadenoma invading the cavernous sinus, four had remnants of pituitary adenoma invading the cavernous sinus, one had empty sella with no evidence of adenoma on the floor of sella turcica, and two had normal pituitary imaging. No patient was hyperprolactinemic and three (Nos 1, 9 and 10) had glucose intolerance. Individual demographic and clinical data are reported in Table 1.

Any drug treatment aimed at decreasing GH hypersecretion (except those of the study procedure) or potentially capable of interfering with GH secretion was withdrawn at least 8 weeks before the start of the study, as part of periodic off-treatment evaluation of the disease, whereas substitutive treatment with L-thyroxine and cortisone acetate was regularly carried out in patient No. 7.

Each patient gave informed consent after full explanation of the purpose of the study, which was approved by the ethics committee of our hospital, and the procedures followed were in accordance

with the Helsinki Declaration of 1975 as revised in 1983.

Procedure

Only somatostatin analog-sensitive patients were enrolled – that is, those showing a reduction in GH greater than 50% of the basal value after the acute s.c. administration of 100 μg octreotide.

Chronic treatment with LSR (Ipsen-Beaufour, Milan, Italy) was carried out with an individually tailored schedule for 6–24 months (Table 2). With the aim of obtaining the maximal GH/IGF-I suppression, the starting schedule of 30 mg i.m. every 14 days was adjusted at 2-month-intervals according to GH/IGF-I values, by shortening the interval between drug administrations to 10 days and, later on, to 7 days, or increasing it to 21 days when GH/IGF-I remained pathological or became less than 50% of the upper limit of normal range (%ULNR) respectively.

Table 2 Long-acting treatment with somatostatin analogs.

Patient no.	LSR		OC-LAR Dosage§
	Duration†	Schedule‡	
1	12	7	30
2	12	7	30
3	6	7	30
4	12	7	30
5	15	14	10
6	12	10	20
7	10	7	30
8	24	21	10
9	12	7	30
10	12	14	10
11	12	7	30
12	10	10	20

†Months of treatment; ‡days between injections; §OC-LAR dosage in the last three cycles of the study period.

After treatment with LSR, the patients were changed directly to treatment with OC-LAR (kindly supplied by Novartis, Milan, Italy), without wash-out. OC-LAR was administered i.m. at 28-day intervals on six occasions, at dosages of 20 mg for the first three times and 10 or 30 mg for the last three times, increasing or decreasing the dosage according to the individual IGF-I response, as described above.

Control measurements were performed on an out-patient basis, at 56–60-day intervals during LSR and, with OC-LAR, at 28-day intervals during the first three cycles and then at the end of the 6th cycle. Every control was performed on the same day as the administration of the drug, before the injection was given, with a careful clinical evaluation and blood analysis.

Blood samples were collected in the morning hourly for 3 hours, after an overnight fast and rest, while the patients were supine and awake, with an indwelling needle inserted in an antecubital vein and kept patent by slow infusion of saline. GH concentrations were assayed on each sample (in the results section the reported value is the mean of the three samples) and IGF-I, glucose and glycated hemoglobin (HbA_{1c}) on the first sample. Ultrasound examination of the gallbladder was performed at 6-month-intervals.

Methods

Glucose and HbA_{1c} were assayed with standard methods (glucose oxidase and HPLC respectively).

GH (Sorin, Saluggia, Italy) and IGF-I (Nichols, San Juan de Capistrano, California, USA) were assayed in duplicate by DELFIA and RIA after acid-ethanol extraction, respectively. The limit of detection of GH was 0.1 µg/l. Standards were calibrated against 1st IS 80/505 (1 ng = 2 IU) for GH, and WHO 87/518 for IGF-I. Intra- and interassay coefficients of variation were 3.5 and 5.5% for GH, 3.7 and 7.2% for IGF-I. Normal values for IGF-I in our laboratory are 114–492 µg/l in patients 25–39 years old, 90–360 µg/l in patients 40–54 years old and 71–290 µg/l in patients older than 55 years.

Statistical analyses

Values are expressed as means ± S.E. IGF-I concentrations are expressed both as absolute values and as %ULNR (age-adjusted).

Data were analyzed by *t*-test, repeated measures analysis of variance followed by Student–Newman–Keuls test, Spearman correlation test, or Fisher exact test, as appropriate.

Values of *P* less than 0.05 were considered significant.

Results

LSR treatment

GH decreased from 41.6 ± 14.6 µg/l to 7.2 ± 1.5 µg/l (*P* = 0.018) at the end of treatment, whereas IGF-I

values declined from 959 ± 94 µg/l to 460 ± 61 µg/l (*P* < 0.00001), expressed as absolute values, and from $287 \pm 30\%$ to $137 \pm 19\%$ expressed as %ULNR. LSR obtained a stable control of the disease – that is, no significant changes in GH/IGF-I concentration were observed between the last two control measurements. The neuroradiological control performed at the 12th month showed a more than 30% shrinkage of the adenoma compared with its size at the baseline imaging, in three patients (Nos 4, 9 and 10) whose primary treatment was with somatostatin analogs.

OC-LAR treatment

After the first three cycles, GH values were 5.4 ± 1.2 µg/l (*P* = 0.05 compared with data from LSR) and IGF-I 469 ± 70 µg/l (not different from data on LSR) ($140 \pm 23\%$ as %ULNR).

At the end of the 6th cycle, no further decline was observed in GH values (5.1 ± 1.1 µg/l), whereas IGF-I values declined to 374 ± 60 µg/l (*P* = 0.05 compared with LSR and compared with data after the 3rd cycle on OC-LAR) ($112 \pm 19\%$ expressed as %ULNR).

Dosages (Table 2)

LSR was administered every 7 days in seven patients (Nos 1–4, 7, 9 and 11), every 10 days in two patients (Nos 6 and 12), every 14 days in two patients (Nos 5 and 10), and every 21 days in one patient (No. 8).

In the last three cycles of the study, OC-LAR dosages were decreased to 10 mg/cycle in three patients (Nos 5, 8 and 10), and increased up to 30 mg in seven patients (Nos 1–4, 7, 9 and 11).

Comparison between LSR and OC-LAR (Fig. 1)

Individual GH concentrations decreased to less than 2.5 µg/l in one patient (No. 8) during LSR and in four patients (Nos 6, 8, 10 and 12) during OC-LAR treatment. During both treatments, the variability among GH concentrations in the three samples collected at each time point was very low (data not shown), being 0.5–1 µg/l in most sensitive patients (Nos 1, 4, 5, 6, 8 and 10–12).

LSR treatment achieved normal age-adjusted IGF-I concentrations in four patients (Nos 5, 8, 10 and 11). OC-LAR achieved normal IGF-I concentrations in five patients (Nos 4, 5, 8, 10 and 11), in three of them (Nos 5, 8 and 10) with 10 mg/cycle, and near-normal (i.e. < 110%ULNR) in three other patients (Nos 1, 2 and 12).

Side effects

No relevant side-effect was recorded during either LSR or OC-LAR treatments. Fasting plasma glucose and HbA_{1c} concentrations did not change during either LSR or OC-LAR treatment (data not shown). At ultrasound

Figure 1 Individual GH concentrations (a) and IGF-I concentrations expressed as %ULNR (b) during LSR and OC-LAR treatment. □, hormonal value obtained during LSR; ○, hormonal value achieved during OC-LAR, for each patient. The horizontal line is set at 2.5 µg/l in (a) and at 100%ULNR in (b).

examination, no gallstone was observed either before or during either somatostatin analog treatments.

Discussion

Somatostatin analogs have dramatically improved medical treatment in acromegaly. The multiple (twice or three times daily) injection schedule has achieved a reasonable control of acromegaly in most patients, with normalization of GH and IGF-I concentrations in 30–60% of treated patients and a reduction in tumor size in 20–50% (6, 7). Continuous s.c. infusion of octreotide controlled the escalation of hormonal concentrations that occurred 6–8 h after individual injections, obtaining a better control of the disease, often with lower daily doses of the drug, but with the burden of discomfort (8). The development of the long-acting somatostatin analog LSR has allowed stable control of acromegaly by means of injections administered at 10–14-day intervals (3, 9). Nowadays, OC-LAR is known to

be very effective with a once-monthly administration schedule (5). Our study is the first that aimed to compare directly the two available long-acting somatostatin analogs in the same series of acromegalic patients.

Our data show that OC-LAR treatment achieves a tighter control of hormonal concentrations as compared with LSR; indeed, in our series, OC-LAR achieved a greater suppression of GH and IGF-I values. Even though the difference in mean values between the two drugs might not seem to be relevant, safe GH concentrations (<2.5 µg/l (10)) and normal or near normal (<110%ULNR) IGF-I concentrations were indeed reached in a greater proportion of patients (33% compared with 8% for GH and 66% compared with 33% for IGF-I) during OC-LAR.

Lanreotide and octreotide exert their effects on GH secretion by coupling to the same pituitary somatostatin receptors (SST-R) of the subtypes 2 and 5 (11), showing similar affinity and binding properties. Therefore, the finding of unequal GH/IGF-I suppression during these two different treatments points to a more powerful or more prolonged inhibition, or both, of GH secretion by OC-LAR administration and consequently a greater extent of IGF-I normalization.

The results obtained in our patients during LSR treatment are far less satisfactory than those previously reported in other series (3, 9). Even though a marked decline of hormonal values was observed, our values for normalized GH and IGF-I concentrations are low, in spite of the shorter interval of drug administration (at 7–10 days in most patients) as compared with the scheduled prescription. This result may reflect the small size of the series and on our having adopted the tighter criteria of cure for acromegaly that have been recommended in the past few years (1) – that is, GH concentrations less than 2.5 µg/l (10), and IGF-I matched for age (12).

The analysis of individual response to the two somatostatin analogs shows heterogeneous responses: some patients (Nos 5, 8 and 10) were very sensitive to somatostatin analogs, achieving normalization of IGF-I values with the 14–21-day schedule during LSR treatment and during 10 mg OC-LAR treatment, whereas others (Nos 3, 7 and 9) showed a lower degree of sensitivity to somatostatin analogs, as pathological GH and IGF-I concentrations persisted even with the highest OC-LAR dosages (30 mg).

The study design (direct switch from LSR to OC-LAR without wash-out) could impose a major criticism on the evaluation of our results. Indeed, in acromegaly it is a well-known phenomenon that chronic treatment with somatostatin analogs induces a progressive increase in GH/IGF-I suppression (13), so that the greater hormonal inhibition during OC-LAR treatment could be partially dependent on this finding, a carry-over effect of LSR treatment, or both. However, all patients had undergone a very prolonged (median 12 months) LSR treatment at individually tailored dosages,

that had attained the maximal GH/IGF-I inhibition, as demonstrated by the lack of any changes in hormonal values between the last two control measurements performed during LSR treatment. Therefore, we believe that the further GH/IGF-I suppression with the short OC-LAR treatment (6 months) can be attributed, with confidence, to this drug alone.

An unexpected finding of our study was that, in the patients most sensitive to these new long-acting somatostatin analogs – those in whom GH values are less than 2.5–3 µg/l and IGF-I are normal or near normal – the assessment of GH concentrations revealed very stable values. Indeed, the analysis of variability of GH values among the three samples collected in each patient at each time point of the study procedure showed that, the lower were the hormonal values, the lower was the magnitude of variability. It is still being debated how many samples should be taken for evaluation of the degree of GH hypersecretion in acromegalic patients, even during medical treatment. In the common clinical setting of outpatients, several samples are usually collected, in the fasting condition and in the first hours of the morning. Even though we did not study the integrated concentrations of GH over a 24-h period (which was beyond the aim of this study), the marked stability of GH concentrations obtained on the three hourly samples during the whole study period in most sensitive patients, together with normal IGF-I values, enable us to hypothesize that long-acting somatostatin analogs flatten the GH secretory spikes that are typical of acromegaly (14), and to suggest that the follow-up of patients with acromegaly can be simplified, relying on a single morning blood sample that assesses both GH and IGF-I.

In conclusion, these preliminary results obtained in a small series show that OC-LAR is able to produce a control of hormonal hypersecretion in acromegaly that is better than that achieved by LSR in a greater number of patients. This drug is a very promising therapeutic tool that improves the compliance of acromegalic patients inasmuch as it can be administered once every 4 weeks.

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