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Long-Term Effects of Depot Long-Acting Somatostatin Analog Octreotide on Hormone Levels and Tumor Mass in Acromegaly*

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ABSTRACT

The effects of a 12- to 24-month treatment with depot long-acting octreotide (OCT-LAR) on hormone profile, tumor mass, and clinical symptoms were reported in 36 patients with active acromegaly [GH, 34.2 ± 5.6 μg/L; insulin-like growth factor I (IGF-I), 784.5 ± 40.4 μg/L]. Fifteen patients were *de novo* whereas 21 had previously undergone unsuccessful surgery.

Serum GH ($P < 0.0001$) and IGF-I levels ($P < 0.0001$) significantly decreased as early as after the first injection of OCT-LAR and progressively declined during the 12–24 months of treatment both in *de novo* and in operated patients. At the last follow-up, GH hypersecretion was controlled (≤2.5 μg/L) in 69.4% whereas normal IGF-I levels were achieved in 61.1% of patients. GH and IGF-I suppression during OCT-LAR treatment was similar in *de novo* and operated patients as shown by nadir GH (2.3 ± 0.6 *vs.* 2.2 ± 0.6 μg/L) and IGF-I (323.1 ± 34.9 *vs.* 275.5 ± 33.0 μg/L), percent suppression of GH (92.7 ± 2.0 *vs.* 85.9 ± 3.3%) and IGF-I (57.4 ± 4.9 *vs.* 61.5 ± 4.6%), and prevalence of GH (73.3 *vs.* 76.2%) and IGF-I (53.3 *vs.* 71.4%) control. A decrease in tumor volume was observed in 12 of 15 *de novo* patients, whereas no shrinkage was detected in 4 of 9 operated patients. No patient had tumor reexpansion during OCT-LAR treatment. Significant clinical improvement was obtained in all patients; heart rate, systolic blood pressure, and diastolic blood pressure significantly decreased in the entire population. A mild but significant increase of blood glucose levels, followed by a decrease of serum insulin levels, was observed after 3 months of treatment: this effect subsided with treatment continuation. OCT-LAR treatment was well tolerated by most patients.

In conclusion, long-term treatment with OCT-LAR was effective in controlling GH and IGF-I hypersecretion in most patients with acromegaly, when applied either as primary therapy or as adjunctive therapy after surgery. Tumor shrinkage was observed in *de novo* patients during OCT-LAR treatment, suggesting that it can be successfully applied as primary therapy in patients bearing invasive tumors, who are less likely to be cured after surgery. (*J Clin Endocrinol Metab* **86:** 2779–2786, 2001)

PHARMACOTHERAPY WITH SOMATOSTATIN analogs is currently regarded as a potential option for the primary therapy of acromegaly. In fact, sc octreotide (OCT) administration in *de novo* acromegalic patients induced suppression of GH and insulin-like growth factor I (IGF-I) levels that was similar to that observed in patients who received OCT treatment after surgery (1). This finding has opened the question of the best treatment strategy in acromegaly. The availability of the slow-release formulation of OCT (OCT-LAR) has further improved the medical approach to this systemic disease. OCT-LAR was developed to enable once-monthly administration, producing stable blood concentrations of the drug, resulting in sustained GH and IGF-I suppression (2). In a dose-ranging study, OCT-LAR was shown to suppress GH and IGF-I levels to a similar extent as the sc formulation in 21 acromegalic patients (3). In a multicenter study, OCT-LAR administered im at 4-week intervals to 151 patients responsive to sc OCT, induced control of GH (≤2.5 μg/L) and IGF-I secretion in 69.8% and 65.8% *vs.* 65.8% and 63.1% during prior treatment with sc OCT, respectively (4). Similar data have been reported in small series of patients treated for 12–36 months (5–8). Systemic and local tolerability as well as patients' compliance were reported to be very good (4–8).

Because data concerning the long-term efficacy of this drug, mostly on tumor mass, are still scant, we investigated the effects of a 12- to 24-month OCT-LAR treatment on hormone profile, tumor mass, and clinical symptoms in 36 acromegalic patients. The potential difference in applying OCT-LAR treatment as primary therapy or after surgery was also investigated.

Patients and Methods

Patients

Thirty-six patients with active acromegaly (21 women and 15 men; age range, 24–77 yr; median, 56 yr) and never treated before with somatostatin analogs, except for a short (≤3 months) treatment before surgery, were enrolled into the study after their informed consent had been obtained. Twenty-one patients had previously undergone unsuccessful surgery. The laboratory diagnosis of acromegaly was defined by high serum GH levels (34.2 ± 5.6 μg/L; mean ± SEM) during a 6-h time course, not suppressible below 2 μg/L after a 75-g oral glucose tolerance test (oGTT) and high plasma IGF-I levels for age (784.5 ± 40.4 μg/L) (9).

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Two patients suffered from overt diabetes mellitus and did not receive oGTT. The presumed duration of acromegaly was assessed by comparison of patients' photographs taken during a one- to three-decade span and by interviews to estimate the date the onset of acral enlargement. In this series, disease duration ranged between 5 and 35 yr (16.9 ± 1.4 yr). The patients' profile at study entry is shown in Table 1. To improve the clinical conditions (10), 16 of the 21 patients operated on had received somatostatin analog treatment with sc OCT at a dose of 0.1 mg three times a day (5 patients), lanreotide at a dose of 30 mg every 14 days (8 patients), and OCT-LAR at a dose of 20 mg every 28 days (3 patients): in these patients the assessment of disease activity was performed at least 3 months after surgery. The only exclusion criteria for *de novo* patients was the presence of visual field defects or other neurological symptoms due to tumor mass.

Study protocol

At study entry plasma IGF-I levels were assayed twice in a single sample, whereas the value of serum GH was calculated as the mean of a 6-h blood sampling (0800–1400 h with 30-min sampling). During treatment, the final GH level was calculated as the average value from at least three blood samples collected, at 15-min intervals, the morning before the next injection of OCT-LAR. At this time point, plasma IGF-I concentrations were assayed as single sampling. Hormonal and clinical evaluations were carried out before, monthly for the first 3 months, and quarterly during the treatment. Hormone normalization after OCT-LAR treatment was considered when basal GH values were 2.5 μg/L or lower as fasting sample or 1 μg/L or lower after glucose load, together with IGF-I values within the normal range for age (11, 12). Blood pressure was measured at study entry and quarterly during OCT-LAR treatment in the right arm, with the subjects in a relaxed sitting position. Before and after 12 and 24 months of treatment, the average of six measurements (three taken by each of two examiners) with a mercury sphygmomanometer was taken. Hypertension was diagnosed when diastolic blood pressure (DBP) values were more than 90 mm Hg and was graded as mild when between 91 and 104 mm Hg, moderate when 105–114 mm Hg, and severe when more than 115 mm Hg, in line with WHO criteria (13). Among the 36 patients, 13 (36.1%) had mild hypertension. Fasting glucose, triglycerides, and total cholesterol levels were measured by standard procedures. At study entry impaired glucose tolerance was diagnosed after oGTT (75 g glucose diluted in 250 mL saline solution, measuring blood glucose every 30 min for 2 h). Diabetes mellitus was diagnosed when fasting glucose was above 7 mmol/L at two consecutive measurements or when 2 h after the oGTT, glucose was 11.1 mmol/L or higher (14). Impaired glucose tolerance was diagnosed when glucose was between 7 and 11.1 mmol/L 2 h after the oGTT with an additional value 11.1 mmol/L or lower between 0 and 2 h after the oGTT (14). Among the 36 patients, 2 (5.5%) had diabetes mellitus and 6 (16.7%) had glucose intolerance. Fasting insulin levels were also measured in all patients. In all patients gallbladder and biliary system ultrasonography was performed before and every 6 months during OCT-LAR treatment.

Treatment protocol

All patients, but the 16 who were treated with somatostatin analogs before surgery, received an acute test with sc OCT at a dose of 0.1 mg to investigate individual patient tolerability to somatostatin analogs (15). In all patients OCT-LAR was initially administered im at a dose of 20 mg every 28 days for 3 months. Then, the dose of OCT-LAR was increased to 30 mg every 28 days on the basis of GH levels above 5 μg/L in 15 patients (16). After 12 months of treatment the dose of OCT-LAR was further increased to 40 mg every 28 days in seven patients (1, 2, 18, 20, 21, 27, and 29; Table 1) and was decreased to 10 mg every 28 days in two elderly patients (14 and 15; Table 1) who achieved fasting GH levels below 1 μg/L. At the end of the study, the dose of OCT-LAR was 10 mg in 2 patients (5%), 20 mg in 14 patients (38.9%), 30 mg in 11 patients (30.5%), and 40 mg in 8 patients (22.2%) (Table 1). One man died of a heart attack 2 months after beginning therapy, and two women died during the follow-up: the former after 48 months of treatment for uterus carcinoma at the age of 58 yr, and the latter after 30 months of treatment for cachexia due to the nutritional problems caused by hesofageal acalasia at the age of 81 yr. Thirty-five patients completed the 12-month follow-up, 32 patients completed the 18-month follow-up, and 28 patients completed the 24-month follow-up (Table 1).

Assays

Serum GH levels were measured by immunoradiometric assay (IRMA) (HGH-CTK-IRMA; Sorin, Saluggia, Italy). The sensitivity of the assay was 0.2 μg/L; 1 μg/L corresponds to 2.5 mU/L. The intra- and interassay coefficients of variation (CV) were 4.5% and 7.9%, respectively. Plasma IGF-I was measured by IRMA after ethanol extraction using DSL kits (Diagnostic Systems Laboratories, Inc., Webster, TX). The sensitivity of the assay was 0.8 μg/L. The intra-assay CV were 3.4%, 3.0%, and 1.5% for the low, medium, and high points on the standard curve, respectively. The interassay CV were 8.2%, 1.5%, and 3.7% for the low, medium, and high points on the standard curve. Fasting GH levels were considered above the normal range when higher than 2.5 μg/L. In our laboratories the normal IGF-I range in 20–30, 31–40, 41–50, and over 50-yr-old subjects was 110–502, 100–494, 100–303, and 78–258 μg/L, respectively.

Magnetic resonance imaging (MRI) studies

MRI studies were performed on clinical 0.5T and 1T scanners, using T1-weighted gradient recalled-echo (repetition time, 200–300 milliseconds; echo time, 10–12 milliseconds; flip angle, 90 degree, four signal averages) in the sagittal and coronal planes. In each measurement 7–11 slices were obtained, with a slice thickness of 2–3 mm and an in-plane spatial resolution of 0.7–0.97 mm (the matrix was 192–256 × 256 on a field of view of 24–25 cm on the sagittal plane and 160–256 × 256 on a field of view of 18–20 cm in the coronal plane). The acquisitions were repeated before and after the administration of 0.1 mmol gadolinium chelate (diethylene-triamine pentacetate). MRI was performed before and after 3, 6, 12, and 24 months of OCT-LAR treatment in *de novo* patients and before and after 12 and 24 months in operated patients. In *de novo* patients shrinkage was established on tumor volume calculated by the Di Chiro and Nelson formula: volume = height × length × width × π/6 (17) and on the maximal tumor diameter, whereas in patients previously operated on shrinkage was established only on the maximal tumor diameter. Tumor shrinkage was evaluated as a reduction of the pretreatment tumor volume or maximal tumor diameter, respectively, in a semiquantitative way as: less than 25% or less than 10%, no shrinkage; 26–50% or 11–20%, mild shrinkage; 51–75% or 21–30%, moderate shrinkage; more than 75% or more than 30%, notable shrinkage. The radiologist (S.C.) was blind in respect to the status of the patient.

Visual perimetry

In all patients the assessment of visual field defects, by Goldmann-Friedmann perimetry, and visual acuity was performed at baseline. The ophthalmologic examination was repeated every 6 months during the follow-up in the patients with visual disturbances.

Statistical analysis

The statistical analysis was performed by means of an SPSS, Inc. (Cary, NC) package. The effect of OCT-LAR was analyzed by the paired Student's t test, ANOVA, χ^2 test, and linear regression analysis, where appropriate. Data are reported as mean ± SEM.

Results

Effect of long-term OCT-LAR treatment on GH and IGF-I levels

A significant decrease of circulating GH (from 34.2 ± 5.6 to 12.5 ± 2.5 μg/L, $P < 0.0001$) and IGF-I levels (from 784.5 ± 40.4 to 582.2 ± 42.1 μg/L, $P < 0.0001$) was observed early after the first injection of OCT-LAR. At this time point, GH and IGF-I decrease was similar in the 16 patients who received the short presurgical treatment with somatostatin analogs and the remaining patients (data not shown). Serum

TABLE 1. Patients' profile at study entry, and effect of long-term treatment with OCT-LAR, maximal dose, and treatment duration

Patient no., sex, age	Serum GH levels[a] (μg/L)		Serum IGF-1 levels (μg/L)		IGF-I level on the upper limit of age-related normal range (%)		Tumor at MRI	Shrinkage (%)	Maximal dose (mg)	Treatment duration (months)	Notes
	Basal	Nadir	Basal	Nadir	Basal	Nadir					
De novo patients											
1 F, 24	121	2.5	1080	320	115	−37	I, S, rP macroadenoma	53.5	40	24	Hair loss
2 F, 25	24.8	8	583	467	16	−7	I,S, rlP macroadenoma	54.9	40	24	No
3 M, 39	89.3	1.6	780	232	57.9	−53	I,S macroadenoma	67.8	20	15	No
4 F,43	77.5	0.8	1289	250	325	−17	I,S macroadenoma	78.8	20	18	No
5 F, 44	20	0.7	697.2	221	130	−27	Microadenoma	18.0	20	18	Hair loss
6 F, 46	91	0.7	1220	410	303	35.3	I,S, rlP macroadenoma	40.6	30	18	No
7 M, 50	63	1.2	780	350	157	15.5	I,S macroadenoma	20.0	30	15	No
8 M, 52	28.6	2.5	545	300	111	16.3	I,S, rlP macroadenoma	35.0	30	16	No
9 F, 53	12.4	1	520	250	101	−3	Microadenoma	100.0	20	24	Died from cancer of the uterus
10 F, 54	26.3	3.0	1092	490	323	85.9	I,S, macroadenoma	21.6	30	18	No
11 M, 57	43	1	612	300	137	16.3	I,S, macroadenoma	61.5	20	24	No
12 F, 61	46.7	6	1063	550	312	131.2	I,S, macroadenoma	33.7	30	24	Diabetes mellitus
13 M, 62	148	3	1221	410	373	58.6	I,S, rlP macroadenoma	62.7	30	24	Diabetes mellitus
14 F, 70	11.5	1	430	110	66.7	−57.4	Microadenoma	100.0	20	24	No
15 F, 77	22.7	0.7	1008	100	290	−61.2	I, S, macroadenoma	48.7	20	24	Hesofageal acalasia; died from nutritional problems
Mean ± SEM	55.1	2.6	861.3	335.1	187.8	6.4		53.1			
	10.8	0.5	75.2	41.1	30.6	14.1		6.8			
Operated patients											
16 M, 27	55.0	0.8	898	170	78.9	−66.1	I-, S, and lP remnant	23.5	30	24	No
17 M, 30	11.0	1.2	570	310	13.5	−38.2	small I remnant	n.e.	30	24	No
18 F, 33	14.1	5.5	495	340	0.2	−31.2	I and S remnant	0	40	24	Pregnancy
19 M, 43	21.0	12.0	650	300	114	−1	I and S remnant	0	30	24	Renal failure needing transplantation
20 F, 44	23.5	2.1	840	750	165	147	I-, S, and lP remnant	23.8	40	24	No
21 M, 46	26.0	3.0	990	400	267	32	Small I remnant	n.e.	40	24	No
22 M, 46	7.3	0.5	520	106	71.6	−65	Empty sella	n.e.	20	24	No
23 F, 56	5.0	0.5	729	210	182	−18.6	Empty sella	n.e.	20	24	Cheratitis after surgery
24 F, 56	15.5	2.6	847	303	282	17.4	I remnant	28.6	30	24	Hysterectomy
25 F, 57	5.0	1.5	460	210	78.3	−18.6	Small I remnant	n.e.	20	24	No
26 M, 58	31.5	0.4	766	210	196.9	−18.6	I, and S remnant	0	20	24	No
27 M, 59	10.6	3.9	1093	400	323.6	55	I-, S, and rlP remnant	8	40	24	Operated for huge goiter
28 F, 59	44.0	2.0	678	250	162.8	−3.1	Empty sella	n.e.	30	24	No
29 F, 60	23.0	2.0	586	280	127.1	−8.5	Small I remnant	n.e.	40	24	Hepatic failure
30 F, 61	7.5	1.0	968	200	275.2	−22.4	I and S remnant	16.2	20	24	No
31 F, 62	29.0	1.0	861	180	233.7	−30.2	Small I remnant	n.e.	20	24	Acute colecystitis
32 M, 66	22.0	1.5	890	200	245	−22.4	Small I remnant	n.e.	20	24	No
33 M, 67	20.0	5.5	880	650	241.1	151.9	I and S remnant	n.e	20	2[b]	Died of heart attack
34 F, 67	4.5	0.5	510	126	97.7	−51.1	I and S remnant	33.3	20	24	Renal failure
35 M, 68	7.7	0.5	537	130	108.1	−49.6	Empty sella	n.e.	20	24	No
36 M, 75	21.0	1.8	552	100	114	−61.2	Small I remnant	n.e.	30	24	Severe atherosclerosis
Mean ± SEM	19.2	2.3	729.5	277.4	160.8	−4.9		14.8			
	2.9	0.6	41.4	36.2	20	13		4.4			

[a] GH values are the mean of at least three samples

[b] Not evaluated due to sudden death from heart attack. The normal GH range was 2.5 μg/L or less. The normal IGF-I range in 20–30, 31–40, 41–50, over 50-yr old subjects was 110–502, 100–494, 100–303, and 78–258 μg/L, respectively. n.e., not evaluated.

GH (3.5 ± 0.7 μg/L, $P < 0.0001$) and IGF-I levels (335 ± 26.2 μg/L, $P < 0.0001$) progressively declined during the first 12 months of treatment both in *de novo* (Fig. 1) and in operated patients (Fig. 2). After 12 months of treatment with OCT-LAR, the percent GH and IGF-I suppression was 83.8 ± 3.2% and 55.2 ± 3.3%, respectively. In the 28 patients treated for 24 months serum GH (from 3.5 ± 0.8 to 2.4 ± 0.5 μg/L, $P = 0.04$) and IGF-I levels (from 333.2 ± 31.2 to 290.1 ± 30.0 μg/L, $P = 0.001$) were further decreased compared with the 12-month follow-up. After 1, 3, 6, 12, 18, and 24 months of OCT-LAR treatment, in the whole population GH hypersecretion was controlled (≤2.5 μg/L) in 16.7%, 34.3%, 60%, 68.6%, 71.8%, and 71.4%, whereas normal IGF-I levels were achieved in 20%, 20%, 42.8%, 48.6%, 56.3%, and 67.8%, respectively. At the last follow-up GH levels were 1 μg/L or lower in 15 patients (41.7%), 1.1–2.5 μg/L in 11 patients (30.6%), 2.6–5 μg/L in 5 patients (14.3%), and higher than 5 μg/L in 5 patients.

At study entry, the 15 *de novo* patients had similar age (50.5 ± 3.8 *vs.* 54.3 ± 2.8 yr) and IGF-I levels (861.3 ± 75.2 *vs.* 729.5 ± 41.4 μg/L) but higher GH levels (55.1 ± 10.8 *vs.* 19.5 ± 3 μg/L, $P < 0.001$) than the 21 patients treated with OCT-LAR after surgery. However, no difference was found in GH and IGF-I suppression during OCT-LAR treatment between *de novo* and operated patients. In fact, nadir GH (2.3 ± 0.6 *vs.* 2.2 ± 0.6 μg/L) and IGF-I (323.1 ± 34.9 *vs.* 275.5 ± 33.0 μg/L) and the percent GH (92.7 ± 2.1 *vs.* 85.9±3.3%) and IGF-I suppression (57.4 ± 4.9 *vs.* 61.5±4.6%) achieved after long-term treatment with OCT-LAR were similar in *de novo* and operated patients as was the prevalence of GH (73.3 *vs.* 76.2%) and IGF-I (53.3 *vs.* 71.4%) control. In 20 patients GH nadir after acute OCT test was available: as expected, nadir GH after acute octreotide administration was higher than during chronic treatment (5.7 ± 1.3 *vs.* 2.4 ± 0.4 μg/L, $P = 0.007$); nadir GH after acute and chronic treatment were significantly correlated each other ($r^2 = 0.32$; $P = 0.0007$).

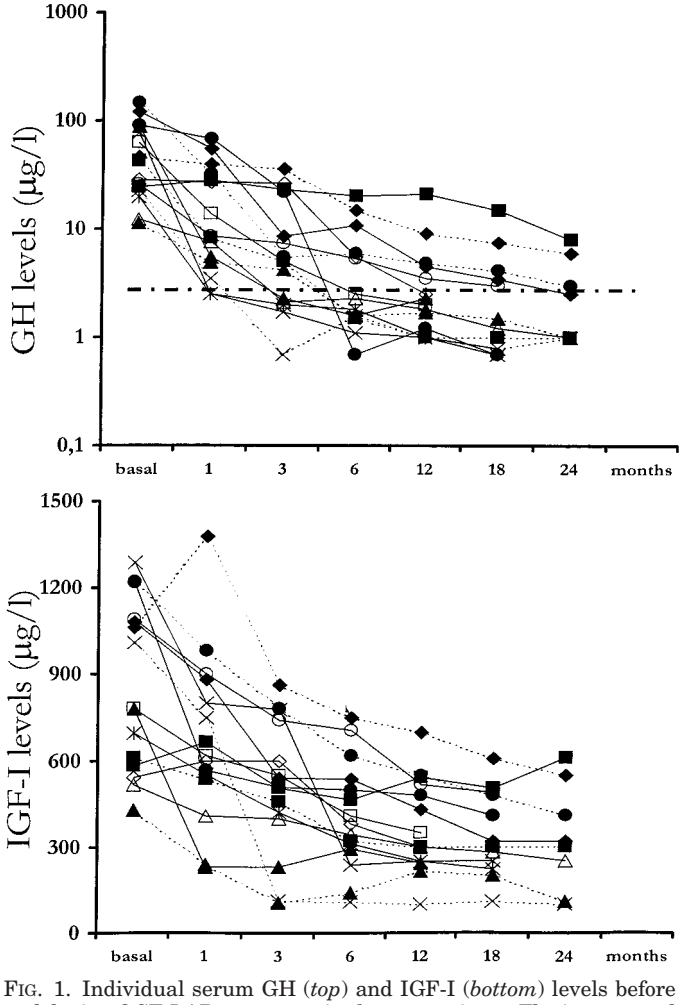

FIG. 1. Individual serum GH (*top*) and IGF-I (*bottom*) levels before and during OCT-LAR treatment in *de novo* patients. The interrupted line indicates the threshold of 2.5 μg/L, which is considered the normal limit for GH levels.

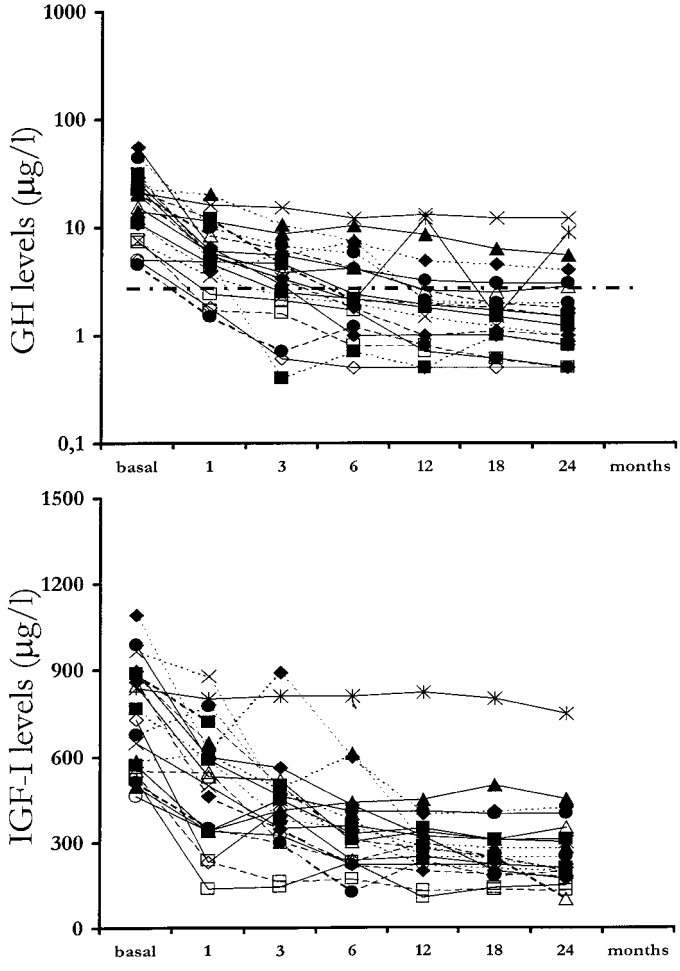

FIG. 2. Individual serum GH (*top*) and IGF-I (*bottom*) levels before and during OCT-LAR treatment in patients subjected to surgery before starting OCT-LAR treatment. The *interrupted line* indicates the threshold of 2.5 μg/,L which is considered the normal limit for GH levels.

Effect of 12–24 months of OCT-LAR treatment on tumor shrinkage

A remarkable decrease in tumor volume was observed in *de novo* patients during OCT-LAR treatment (Fig. 3). After 3 months only five patients had a mild-to-moderate shrinkage.

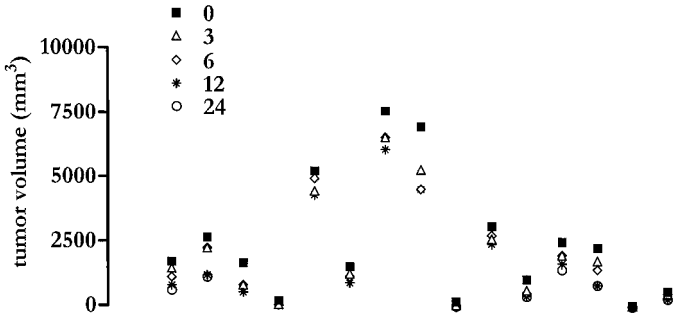

FIG. 3. Individual values of tumor volume before and during OCT-LAR treatment in *de novo* acromegalic patients, shown in order of age as in Table 1.

In contrast, at the last follow-up shrinkage was absent in three patients (20%), mild in three (20%), moderate in six (40%), and notable in three patients. Two patients with microadenoma had disappearance of their tumors after 6–12 months of treatment. In one patient with microadenoma a remarkable tumor decrease was observed after 3 months of OCT-LAR treatment at a dose of 20 mg every 28 days (Fig. 4). Tumor shrinkage was evaluated in only 9 of the 21 operated patients (Table 1): shrinkage was absent in 4, mild in 1, moderate in 3, and notable in 1 patient. After 12 and 24 months of treatment, no difference was found in the maximal tumor diameter both in the eight *de novo* (11.1 ± 2.7 *vs.* 10.3 ± 2.5 mm) and in the nine operated patients (10.7 ± 2.2 *vs.* 10.2 ± 2.2 mm). At the last follow-up, the decrease in the maximal tumor diameter was slightly but not significantly higher in *de novo* (31.1 ± 7.6%) than in operated patients (14.8 ± 4.4%). In *de novo* patients, no correlation was found between tumor volume and age, disease duration and baseline GH and IGF-I levels, or between the percent tumor reduction and percent GH/IGF-I suppression or the dose of OCT-LAR. No patient had tumor reexpansion during OCT-LAR treatment. No *de novo* patient had visual field defects at study entry whereas 4 of the 21 operated patients had temporal quadrantopsia that did not significantly improve during OCT-LAR treatment.

Effect of 12–24 months of OCT-LAR treatment on clinical symptoms and biochemical data

All patients obtained significant clinical improvement during OCT-LAR treatment: specifically, patients reported improvement of headache (n = 10), hyperhidrosis (n = 15), asthenia (n = 5), and osteo-articular pain and mobility (n = 22). Reduction of soft tissue swelling was noted by all patients. In addition, during treatment, heart rate [from 92.1 ± 1.6 to 86.0 ± 1.2 beats per minute (bpm) after 12 months and 83.9 ± 1.6 bpm after 24 months, $P < 0.01$], systolic blood pressure (from 138.6 ± 1.5 to 134.4 ± 1.2 mm Hg after 12 months and 132.4 ± 1.5 mm Hg after 24 months, $P < 0.01$), and DBP (from 88.9 ± 1.1 to 86.3 ± 0.9 bpm after 12 months and 84.9 ± 1.0 bpm after 24 months, $P < 0.05$) significantly decreased in the population as a whole. Among the 13 patients with mild hypertension, only 3 still had DBP above 90 mm Hg and remained under specific antihypertensive treatment. The patient who died of a heart attack had mild hypertension and was specifically treated at study entry. No difference was observed in the clinical improvement between *de novo* and operated patients. Similarly, with the exclusion of the two diabetic patients, no difference was found in blood glucose, triglycerides, and total cholesterol levels before and after 12–24 months of treatment, although a mild but significant increase of blood glucose levels (5.3 ± 0.3 *vs.* 5.9 ± 0.2 mmol, $P < 0.05$) followed by a decrease of serum insulin levels (17.7 ± 3.4 *vs.* 10.5 ± 3.1 mU/L, $P < 0.05$) was observed after 3 months of treatment. However, at the end of OCT-LAR treatment blood glucose (5.5 ± 0.3 mmol/L) and insulin (15.0 ± 3.2 mU/L) were similar to pretreatment values. Both diabetic patients reduced insulin requirements during OCT-LAR treatment, and one of the six patients with impaired glucose tolerance required additional treatment with glucose-lowering drugs.

Tolerability

OCT-LAR treatment was well tolerated by most patients: abdominal discomfort was reported by 10 (27.8%), steatorrhea by 4 (11.1%), flatulence by 10, and hair loss by 4 patients. These side effects spontaneously disappeared in seven cases and after treatment with pancreatic enzymes in the others. Hair loss stopped after 3–6 months. Asymptomatic gallstones were detected in two patients whereas in another patient colecystectomy for acute colecystitis was performed after 12 months of treatment. This latter patient was withdrawn from OCT-LAR treatment.

Discussion

Acromegaly is a chronic and slowly developing disease that causes progressive disability and shortens life (18, 19). Its optimal treatment is the selective removal of the GH-secreting pituitary adenoma, which should, consequently, result in the normalization of GH and IGF-I secretion, without causing secondary hypopituitarism and with minimal side effects and morbidity. *Trans*-sphenoidal surgery seems to be the most appropriate therapeutic measure and is associated with very low morbidity and a low recurrence rate (20–22). However, the results of surgery reported from many centers over the last 20 yr are difficult to compare with our practice because the criteria used to define the control of acromegaly have changed (12) and the success of surgery has improved with the increasing experience of pituitary surgeons and the improvement in surgical technique (23). However, in one recent series of 115 patients undergoing *trans*-sphenoidal surgery (20), remission after surgery alone was achieved in 61%, but in only 53% of patients with macroadenoma. A similar result was reported by Swearingen *et al.* (21). Therefore, it is presently accepted that disease control after surgery alone can be achieved in a high proportion of cases with relatively small enclosed adenomas (11, 24, 25). In patients with invasive adenomas it is, therefore, necessary to use pharmacotherapy to achieve disease control (11, 24, 25). The treatment with somatostatin analogs, particularly OCT (26), has been widely shown to rapidly and effectively reduce GH hypersecretion and to decrease IGF-I concentrations. On

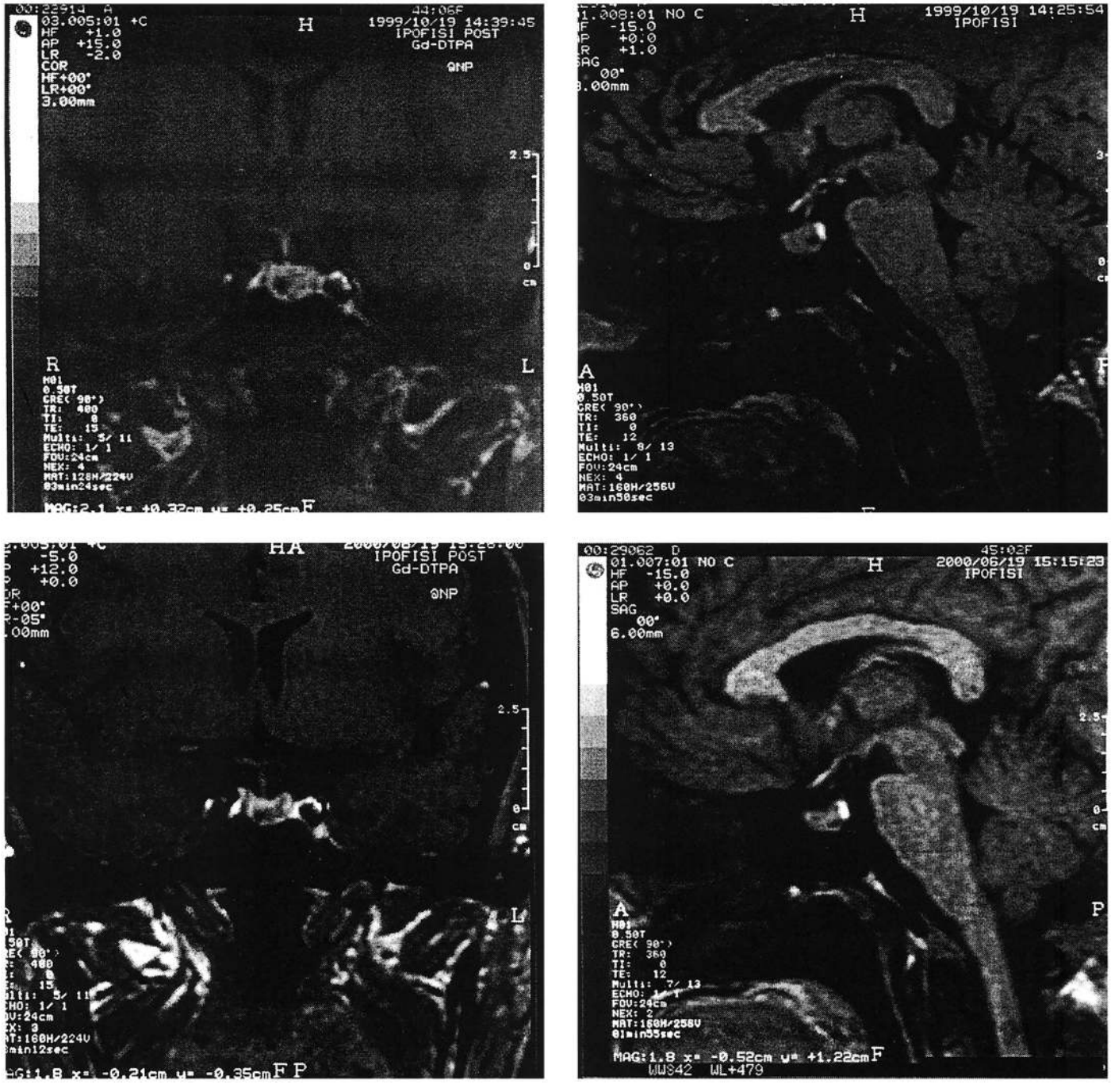

FIG. 4. Coronal (*left*) and sagittal (*right*) sections of a pituitary microadenoma in patient 5 before (*top*) and after (*bottom*) 3 months of OCT-LAR at a dose of 20 mg every 28 days.

the other hand, a recent multicenter study has demonstrated that no difference existed in the GH and IGF-I suppression after sc OCT treatment between patients treated with this drug primarily and those treated after unsuccessful surgery (1). This relevant result has opened the question as to whether surgery should still be considered as primary therapy of all patients with acromegaly. The recent availability of somatostatin analogs provided in slow-release formulations such as lanreotide (27–30), and OCT-LAR (4–8) has further improved patients' compliance to long-term treatment.

In accord with previous studies (4–7), the results of the present study show that treatment with OCT-LAR is highly effective in controlling GH and IGF-I hypersecretion in the majority of acromegalic patients (71.4% and 67.8%, respectively). In particular, a significant decrease of GH and IGF-I levels was noted after the first injection of 20 mg OCT-LAR. Interestingly, although *de novo* patients presented with higher GH levels at study entry than operated patients, the final therapeutic effect of OCT-LAR was identical in these two subgroups of acromegalics. These results confirmed

those reported by Newman *et al.* (1) in a multicenter trial involving a large cohort of patients treated with sc OCT.

Following the decrease of GH and IGF-I levels, significant improvement of clinical symptoms was experienced by the majority of our patients: in particular, they reported improvement in the articular mobility at the hands and knees, and 10 of 11 patients had dramatic improvement of headache. Besides these effects, we observed an early impairment of glucose tolerance that was, however, short-lasting and an overall improvement of blood pressure during OCT-LAR treatment. A clinically insignificant reduction of heart rate was also noted, confirming previous results obtained with sc OCT (31).

One of the most relevant results of this study is that 53.3% of patients treated with OCT-LAR as primary therapy had a moderate-to-notable decrease of tumor volume with an average value of 53.1 ± 6.7% tumor reduction after 12 months of treatment, leading to tumor disappearance in two patients bearing microadenoma at study entry. In *de novo* patients, the shrinking effect of OCT-LAR was progressive during long-term treatment although the most dramatic tumor reduction was observed at the 3-month follow-up (29.8 ± 5.1 after 3 months *vs.* 7.9 ± 3%, 18.8 ± 4.2% and 5.4 ± 3.1% after 6, 12, and 24 months, respectively). The effect on tumor size of OCT-LAR has already been reported to occur in 29–72% of patients (8): however, the majority of these patients had already been treated by surgery and/or radiotherapy. The degree of tumor reduction varied from 20% (3, 32) to 100% (5) and was reported both in micro- and in macroadenomas (8). These results are in line with those observed in our patients. However, in the present study the reduction in the maximal tumor diameter was slightly lower in operated than in *de novo* patients (14.8 ± 4.4 *vs.* 31.1 ± 7.6%). Whether surgical manipulation of the tumor, causing fibrosis and histological changes in tumor tissue, can be considered responsible for the scant shrinking effect of OCT-LAR therapy in remnant tumors or whether the irregularity of the morphology of remnant tumors does not allow a precise estimation by MRI of remnant size cannot be ruled out. A similar result was, however, recorded in another large series of patients treated with lanreotide, another slow-release formulation (33).

The incidence of side effects was scant, and patients' compliance to the long-term treatment was excellent. These results are in agreement with previous studies of shorter duration (4–7). However, one patient was withdrawn from OCT-LAR because of acute colecystitis treated by colecystectomy.

In conclusion, long-term treatment with OCT-LAR was effective in normalizing GH and IGF-I levels in as many as 69.2% and 73.7% of patients with acromegaly, respectively, without any difference when applied as either primary therapy or as adjunctive therapy after surgery. The incidence of side effects during treatment was scant, even in patients treated with 40 mg every 28 days. Interestingly, notable tumor shrinkage was observed in *de novo* patients during OCT-LAR treatment, most evident as early as after 3 months. On this basis, OCT-LAR can be considered as a very effective and well tolerated treatment for acromegaly and can be successfully applied as primary therapy in patients bearing invasive tumors, who are less likely to be cured after surgery. In fact, even considering that the cost of the medical treatment is currently rather elevated, in these patients the global cost of the treatment includes that of the unsuccessful surgery and of the medication.

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