CLINICAL STUDY

Beneficial effect of dose escalation of Octreotide-LAR as first-line therapy in patients with acromegaly

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Abstract

Objective: To evaluate the efficacy of dose escalation of Octreotide-long-acting repeatable (LAR) up to 40 mg/month we studied 56 newly diagnosed patients with acromegaly (24 women, 32 men; age 20–82 years).

Design: Analytical, observational, open and prospective.

Methods: Three months after LAR treatment beginning with a dose of 20 mg/q28d (every 28 days), 24 patients maintained the same dose (Group A), while 32 required a dose of 30 mg/q28d (Group B). The dose was further increased to 40 mg/q28d in 17 out of the 32 patients of Group B for another 12 months (Group C).

Results: After 24 months, serum GH and IGF-I levels decreased by $93.1 \pm 8.6\%$ (95% confidence limit (CL) 90.8–95.4%) and $62.7 \pm 13.4\%$ (95% CL 59.1–66.3%) respectively. Control of GH and IGF-I levels was achieved in 45 patients (80.3%). Tumor shrinkage after 12 months was $49.8 \pm 23\%$; the relative tumor shrinkage during the second 12 months of treatment was $35.3 \pm 13.1\%$ and overall tumor volume was $68.1 \pm 16.5\%$ (95% CL 63.7–72.5%). Glucose tolerance impaired in eight patients (14.3%): four in Group A and four in Group C (16.7% vs 36.4%, $P=0.39$). The final dose was predicted by the patient's age at diagnosis ($t=-2.2$; $P=0.032$) and baseline tumor volume ($t=2.1$; $P=0.043$).

Conclusion: An increase of the LAR dose up to 40 mg/q28d in patients resistant to 30 mg/q28d is followed by greater suppression of GH and IGF-I levels and tumor shrinkage without further significant impairment of glucose tolerance when compared with lower doses. These results suggest that a new dosage schedule of 40 mg every 28 days is applied in patients with acromegaly mostly of young age and with bigger tumors who are likely to be poorly responsive to standard doses of Octreotide-LAR.

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Introduction

Acromegaly is associated with reduced life expectancy chiefly because of cardiovascular (60%) and respiratory diseases (25%) (1). The most predictive survival indices are a post-treatment growth hormone (GH) value <5 mU/l (equal to <2.5 µg/l) associated with insulin-like growth factor-I (IGF-I) in the normal range after any treatment (1).

In the last two decades, somatostatin analogs have been considered a cornerstone of medical therapy for acromegaly. After 12 months of treatment with Octreotide-LAR (LAR), control of GH and IGF-I excess is achieved in 54 and 63% of unselected patients (2) but the proportion of subjects achieving IGF-I normalization is reported to increase significantly with time (3). Clinically significant tumor shrinkage (20–30% versus baseline) has also been reported (4, 5). An average 50% tumor decrease is

achieved when the drug is used exclusively, or before surgery or radiotherapy (5). After 12 months of first-line treatment with somatostatin analogs, we recently reported control of GH levels in 57.6%, of IGF-I levels in 45.5% and a $>50\%$ tumor shrinkage in 44.4% of 99 unselected newly diagnosed patients (6).

The dose of LAR in different studies ranged between 10 and 40 mg every 28 days (q28d). High doses are generally administered in resistant patients who do not control GH and IGF-I excess with lower doses. Some further benefit by LAR dose increase was reported in some studies. Turner *et al.* (7) reported the control of GH and IGF-I levels respectively, in six and five out of the ten patients treated with 20 mg/q28d for 6 months and another two achieved hormone control after increasing the drug dose up to 30 mg/q28d. Similarly, Cozzi *et al.* (8) reported that an up-titration of the LAR dose from 20 to 30 mg in 40 out of 110 patients produced a better

suppression of IGF-I but not of GH levels. We also increased the LAR dose up to 40 mg/q28d in 8 out of 36 patients (23%) because of poor disease control; dose increment was followed by a further decrease of GH and IGF-I levels though they did not normalize during the 24 months of follow-up (9).

Data on dose escalation of Octreotide-LAR in patients with acromegaly are lacking. In the setting of a prospective evaluation of the effect of first-line treatment with LAR, we analyzed the progressive up-titration of LAR on GH and IGF-I levels and tumor volume in patients newly diagnosed with acromegaly treated with LAR for at least 24 months.

Patients and methods

Patients

From 1st January 1995 to 31st December 2004, 56 patients (26 women aged 20–82 years and 30 men aged 21–76 years) with active acromegaly were admitted to this study out of the 271 patients who came to our department for acromegaly during the same period. One-hundred and eighty-five patients were excluded because of: 1) primary surgery in 95 patients; 2) concomitant hyperprolactinemia requiring combined somatostatin analogs and dopamine-agonist treatment in 29 patients; 3) primary treatment with lanreotide in 44 patients (15); and 4) treatment duration being <24 months in 32 patients. Out of these 32 patients, 16 were withdrawn from LAR treatment because of lack of GH and IGF-I control before completing 24 months of treatment, 16 did not complete 24 months because the follow-up was still ongoing. Data of 12-month treatment in 45 patients (6) and those of 24-month treatment (9) have been reported in previous studies. The diagnosis of acromegaly was defined in all of the patients as previously reported (10), by high serum GH levels, not suppressible <1 µg/l after glucose load and high plasma IGF-I levels for age. Based on magnetic resonance imaging (MRI), five patients had a microadenoma, ten had an enclosed macroadenoma, 26 had a macroadenoma with extrasellar extension, and 15 patients had macroadenomas with clear-cut signs of invasion of surrounding structures. The interval between assumed clinical onset and the time of treatment ranged from 24 to 360 months (median 60 months). Table 1 shows patients' profile at study entry.

All patients signed an informed consent to approve diagnostic testing, treatment decision, methods for follow-up, and treatment of the data for scientific purposes. This study has been conducted in accordance with the Helsinki II Declaration on human experimentation. This study is part of a large, prospective study to investigate the effect of first-line surgery or medical therapy (with somatostatin analogs and/or

Table 1 Patients' profile at study entry. Data are shown as mean ± s.d. and 95% CL in parentheses.

No of patients	56
Women/men	24/32
Age (years)	45 ± 18 (40–50)
Disease duration (months)	98 ± 81 (76–119)
Serum GH levels (µg/l)	55.5 ± 44.9 (43.5–67.5)
Serum IGF-I levels (ULN)	2.44 ± 0.72 (2.25–2.63)
Tumor volume (mm ³)	2229 ± 1445 (1842–2816)
Fasting blood glucose levels (mmol/l)	5.4 ± 1.3 (5.1–5.8)
Fasting serum insulin levels (mU/l)	21.2 ± 14.9 (17.3–25.2)
HOMA-R	5.8 ± 6.8 (3.9–7.6)
HOMA-β (%)	55.6 ± 38.4 (45.3–65.9)

dopamine/agonists) on GH, IGF-I, tumor mass, cardiovascular risk markers, cardiomyopathy, hypertension, metabolic profile, and prostate diseases in all the patients coming for a diagnosis of acromegaly in our department and approved by our Ethical Committee on 14th October 1997 (no. 60/97).

Cure criteria

The patients were considered controlled if the fasting mean GH levels were ≤2.5 µg/l in the presence of normal IGF-I levels for sex and age (11). Resistance to LAR treatment was defined as GH levels being > 2.5 µg/l in the presence of IGF-I levels above the gender and age reference range after 12 months of treatment with 30 mg/q28d.

Study design

This is an analytical, observational, 24-month, open, prospective study to investigate the effect of progressive increase of Octreotide-LAR doses in patients newly diagnosed with acromegaly. Primary outcome measures were GH and IGF-I control and tumor shrinkage while the secondary outcome measure was glucose tolerance and tolerability to high doses.

Study protocol

At diagnosis and every 6 months, 24–48 h before changes in treatment doses were applied, the following were measured:

1. Serum IGF-I levels twice in a single sample at the time 0 of the GH profile; GH levels calculated as the mean value of three to six samples drawn every 30 min; the average value was considered for the statistical analysis.
2. Tumor volume on MRI studies performed on clinical 1T and 1.5T scanners using T1-weighted gradient recalled-echo in the sagittal and the coronal planes, as already reported (6, 9, 12). The acquisitions were repeated before and after the

administration of 0.1 mmol gadolinium chelate (diethylene-triamine pentacetate). In all patients, MRI was performed at diagnosis and after 6, 12, and 24 months of treatment. The maximal sagittal, axial, and coronal diameters were measured, then tumor volume was calculated by the De Chiro and Nelson formula ((volume = sagittal $\times$ coronal $\times$ axial diameters) $\times \pi/6$). According to previous studies (6, 9) on post-treatment MRI, tumor shrinkage was assessed as the percent decrease of tumor volume when compared with baseline.

- Glucose tolerance by assaying glucose and insulin levels at fasting. Only at diagnosis glucose and insulin were also measured every 30 min for 2 h after the oral administration of 75 g glucose diluted in 250 ml saline solution. In four patients, the glucose load was not performed because of overt diabetes (fasting glucose was above 7 mmol/l at two consecutive measurements) (13). Diabetes mellitus was diagnosed in another eight patients when 2 h after the oGTT glucose was >11 mmol/l (13). Impaired glucose tolerance (IGT) when glucose level was between ≥ 7.8 and <11 mmol/l, 2 h after the oGTT and/or impaired fasting glucose when glucose level was between 5.6 and 6.9 mmol/l at fasting were diagnosed in 20 patients (13). Glucose tolerance was normal (below 5.6 mmol/l at fasting) in 24 patients. To predict insulin resistance homeostatic model assessment (HOMA)-R (%) and β -cell function (HOMA- β (%)) was used in accordance with Matthews *et al.* (14). By assuming that normal-weight healthy subjects aged <35 years have a HOMA- β of 100% and a HOMA-R of 1, the values for individual patients can be assessed from the insulin and glucose concentrations by the following formulae: $\text{HOMA-R} = (\text{insulin (mU/l)} \times \text{fasting glucose (mmol/l)}) / 22.5$ and $\text{HOMA-}\beta = (20 \times \text{insulin (mU/l)}) / (\text{glucose (mmol/l)} - 3.5)$.

Treatment protocol

Before starting therapy, all patients received an acute test with s.c. Octreotide at a dose of 0.1 mg in the morning after an overnight fast and at least 2 h bedrest, to investigate individual patient's tolerability to somatostatin analogs (15). Then, all patients were treated with Octreotide-LAR i.m. at an initial dose of 20 mg/q28d for three months. Subsequently, LAR treatment was maintained at the same dose in patients achieving GH levels ≤ 2.5 $\mu\text{g/l}$ and IGF-I levels in the normal range (Group A), or increased up to 30 mg every 28 days in patients with IGF-I levels above the normal range and/or GH levels less than or greater than 2.5 $\mu\text{g/l}$. After another 9 months of treatment with 30 mg/q28d, the dose was maintained in 15 patients achieving GH levels ≤ 2 homeostatic

model assessment 5 $\mu\text{g/l}$ and IGF-I levels in the normal range (Group B), while it was further increased to 40 mg/q28d if fasting GH levels were still >2.5 $\mu\text{g/l}$ and/or IGF-I levels were above the normal range (Group C).

Assays

From 1st January 1995 to 31st December 2001, serum GH levels were measured by IRMA (Sorin, Saluggia, Italy); the sensitivity of the assay was 0.2 $\mu\text{g/l}$ and the intra- and inter-assay coefficients of variation (CVs) were respectively 4.5 and 7.9%. From 1st January 2002, serum GH levels were measured by IRMA using commercially available kits (HGH-CTK-IRMA Sorin). The sensitivity of the assay was 0.05 $\mu\text{g/l}$. The intra- and inter-assay CVs were 4.3 and 8.5% respectively. Serum IGF-I was measured by IRMA after ethanol extraction, using Diagnostic System Laboratories Inc. (Webster, TX, USA). The normal range in ≤ 20 , 21–30-, 31–40-, 41–50-, 51–60-, 61–70-, and >70 -year-old men was 180–625, 118–475, 102–400, 100–306,

Figure 1 Profile of GH (top) and IGF-I levels (expressed as times above the upper limit of normal (ULN); bottom) during the study according with the final dose of Octreotide-LAR.

95–270, 88–250, and 78–200 µg/l respectively, whereas in women it was 151–530, 118–450, 100–390, 96–288, 90–250, 82–200, and 68–188 µg/l respectively. The sensitivity of the assay was 0.8 µg/l. The intra-assay CVs were 3.4, 3.0, and 1.5% for low, medium, and high points of the standard curve respectively. The inter-assay CVs were 8.2, 1.5, and 3.7% for low, medium, and high points of the standard curve. IGF-I data are shown as the upper limit of normal range ((ULN) normal ≤ 1).

Statistical analysis

The data were analyzed using MedCalc Software for Windows (MedCalc, Mariakerke, Belgium). Data are reported as mean ± s.d. unless otherwise specified. The comparison between Group A versus Groups B + C was performed using the Mann–Whitney *U* test; two-sided *P* values are reported as exact probability adjusted for ties. The comparison among Groups A, B, and C was performed by Kruskal–Wallis test followed by the Dunn's multiple comparison test. The comparison of the data collected at baseline and during treatment (0 vs 6 vs 12 vs 18 and vs 24 months) was performed by the Kruskal–Wallis test followed by the Dunn's multiple comparison test. The χ^2 test was used to compare categorical variables. The significance was set at 5%. Correlation was analyzed by calculating the Spearman rank correlation coefficient; two-sided *P* values are shown. The multiple regression analysis was performed in order to indicate the best predictor of dose

requirement among baseline characteristics; in this analysis were included only the variables having a Spearman ρ of <0.01.

Results

Octreotide-LAR dosages

Three months after beginning LAR treatment, 24 (42.9%) of the 56 patients maintained a dose of 20 mg mg/q28d (Group A), while 32 (57.1%) required a dose of 30 mg/q28d (Group B); after completion of out 12 months, 17 (53.1%) out of the 32 patients of Group B required further increase of the dose up to 40 mg/q28d for another 12 months (Group C).

Primary outcome measures

Control of GH and IGF-I levels GH and IGF-I levels decreased during LAR treatment (Fig. 1); overall, after 24 months, serum GH and IGF-I levels decreased by $93.1 \pm 8.6\%$ (95% CL 90.8–95.4%) and $62.7 \pm 13.4\%$ (95% CL 59.1–66.3%) respectively. Patients of Groups B and C were younger and had shorter disease duration than those of Group A, while baseline GH and IGF-I levels were similar (Table 2).

After 24 months of treatment, control of GH and IGF-I excess was achieved in all patients of Groups A and B (as expected) and in six patients of Group C (35.3%) so

Table 2 Primary and secondary outcome measures according with the final dose of Octreotide-LAR treatment.

Final dose of Octreotide-LAR	Group A 20 mg	Group B 30 mg	Group C 40 mg	<i>P</i>
No. of patients	24 (42.8%)	15 (26.8%)	17 (30.4%)	
Women/Men	10/17	7/8	9/8	
Age (years)	53 ± 17	37 ± 15 ^A	40 ± 13 ^A	0.003
Disease duration (months)	137 ± 96	63 ± 42 ^A	73 ± 45 ^A	0.003
Baseline GH levels (µg/l)	46.7 ± 49.4	59.5 ± 27.2	65.7 ± 46.4	0.35
Final GH levels (µg/l)	1.1 ± 0.5	1.4 ± 0.4	4.4 ± 3.7 ^B	<0.0001
Final GH decrease (%)	94.0 ± 99	95.8 ± 5.9	90.6 ± 8.3	0.21
Baseline IGF-I levels (ULN)	2.38 ± 0.80	2.32 ± 0.54	2.61 ± 0.67	0.47
Final IGF-I levels (ULN)	0.70 ± 0.1	0.78 ± 0.11	1.22 ± 0.33 ^B	<0.0001
Final IGF-I decrease (%)	69.1 ± 9.6	65.0 ± 7.7	51.2 ± 13.6 ^B	<0.0001
Baseline tumor volume (mm ³)	1189 ± 1198	2130 ± 953 ^{A,C}	2952 ± 1181 ^A	<0.0001
Final tumor volume (mm ³)	535 ± 414	592 ± 334	1342 ± 890 ^B	<0.0001
Final tumor shrinkage (%)	75.3 ± 13.8	71.9 ± 10.7	53.0 ± 15.9 ^B	<0.0001
Baseline glucose levels (mmol/l)	5.8 ± 1.7	5.0 ± 0.5	5.1 ± 0.6	0.073
Final glucose levels (mmol/l)	5.2 ± 0.4	5.3 ± 0.3	5.4 ± 0.3	0.19
Baseline insulin levels (mU/l)	25.5 ± 18.1	16.0 ± 6.5	16.2 ± 9.5	0.039
Final insulin levels (mU/l)	7.7 ± 1.6	7.5 ± 1.4	7.0 ± 1.3	0.31
Baseline HOMA-R	7.7 ± 9.2	3.7 ± 1.8	3.6 ± 2.2	0.063
Final HOMA-R	1.8 ± 0.4	1.8 ± 0.3	1.7 ± 0.3	0.26
Baseline HOMA-β (%)	63.9 ± 37.4	42.7 ± 34.2	45.3 ± 41.8	0.14
Final HOMA-β (%)	9.7 ± 6.5	8.5 ± 5.6	6.3 ± 5.1	0.68
Prevalence of GH control (pts no. (%))	27 (100)	15 (100)	6 (35.3)	<0.0001
Median time to achieve GH control (months)	6	18 ^A	15 ^A	<0.0001
Prevalence of IGF-I control (pts no. (%))	27 (100)	15 (100)	5 (29.4)	<0.0001
Median time to achieve IGF-I control (months)	6	18 ^A	18 ^A	<0.0001

A, *P* < 0.01 versus Group A; B, < 0.01 versus Group A and B; C, < 0.01 versus Group C.

that 45 patients (80.3%) achieved control of GH and IGF-I excess.

At baseline, the 45 patients achieving disease control with any dose, had significantly lower GH levels than the 11 non-controlled (48.7 ± 42.6 vs 82.6 ± 46.4 $\mu\text{g/L}$; $P=0.03$), while IGF-I levels were similar (2.36 ± 0.72 vs 2.78 ± 0.65 ULN; $P=0.065$).

In patients of Groups A and B, suppression of GH and IGF-I levels was significantly higher in the first than in the subsequent 12 months of treatment; no difference was observed in the 17 patients of Group C (Fig. 2).

Tumor shrinkage At baseline, tumor volumes of Group A patients were significantly smaller than those of Groups B and C (Table 2). Overall, after 24 months, the tumor volume was decreased by $68.1 \pm 16.5\%$ (95% CL 63.7–72.5%). Total tumor shrinkage after 24 months was significantly lower in patients of Group C than that of Groups A and B (Table 2, Fig. 3).

Figure 2 Percent suppression of GH (top) and IGF-I levels (bottom) in the Groups A, B, and C from baseline to 12 months of treatment (12), from 12 to 24 months of treatment (24) and total suppression (from baseline to 24 months of treatment). * $P<0.01$ vs 12 months Groups A and B; ** $P<0.01$ vs 12 months suppression in individual groups; *** $P<0.05$ vs 24 months Groups A and B; **** $P<0.05$ vs 12 months Group A; ***** $P<0.05$ vs 12 months Group B.

The partial tumor shrinkage after 12 months was significantly higher in the patients of Group A than that of Groups B and C (Fig. 3).

Patients achieving disease control had smaller tumor volumes at baseline (2021 ± 1078 vs 3079 ± 2318 mm^3 ; $P=0.028$) and achieved a greater tumor shrinkage at end-treatment (72.6 ± 13.8 vs $49.8 \pm 13.9\%$; $P<0.0001$) than those who did not.

Secondary outcome measures

Glucose tolerance At study entry, 24 (42.8%) patients had normal glucose tolerance, 20 (35.7%) had IGT, and 12 (21.4%) had diabetes mellitus; only one patient was receiving metformin treatment at the diagnosis of acromegaly. Groups B and C patients had lower insulin levels and HOMA-R index than those of Group A. During the study, fasting glucose levels significantly increased both in the patients with normal glucose tolerance and in those with IGT, while they decreased significantly in patients with diabetes (Fig. 4). In these latter patients, however, treatment for diabetes was started in the 11 previously untreated patients, four with insulin and seven with metformin. Insulin levels were suppressed in all groups during the study (Fig. 4).

At the end of the study, out of the 24 patients with normal glucose tolerance at diagnosis, six (25%) developed IGT; of the 20 patients with IGT, 14 (70%) remained IGT, two developed overt diabetes (10%) and started a treatment with metformin, and four (20%) normalized glucose tolerance; out of the 12 patients with diabetes eight remained diabetic (66.7%) and maintained their treatment (insulin in five and metformin in three) and four (28.3%) improved to IGT and stopped metformin treatment. HOMA-R and HOMA- β were significantly reduced during treatment

Figure 3 Percent tumor shrinkage in the Groups A, B, and C from baseline to 12 months of treatment (12), from 12 to 24 months of treatment (24) and total tumor shrinkage (from baseline to 24 months of treatment). * $P<0.01$ versus same time Group A; ** $P<0.01$ versus same time Group A and B.

Figure 4 Profile of fasting glucose (top) and insulin levels (bottom) during the study and according with glucose tolerance status at diagnosis.

independently from the dose of Octreotide-LAR used (Table 2) and disease control (data not shown). Of the patients showing impairment of glucose tolerance, four were in Group A and four in Group C (16.7% vs 36.4%, $P=0.39$).

Tolerability Octreotide-LAR treatment was well tolerated by most patients. After the first two to three injections, abdominal discomfort was reported by 36 (64.3%), steatorrhea by eight (14.3%), flatulence by 25 (44.6%), and hair loss by seven women (29.2%). These side effects spontaneously disappeared in all cases except ten (17.9%) who required treatment with pancreatic enzymes for 3–6 months. Hair loss stopped after 3–6 months.

At diagnosis, asymptomatic gallstones were detected in 15 patients, while at end-treatment they appeared in another 15 patients (26.8%).

Correlation analysis

The final LAR dose was significantly correlated with the patients' age at diagnosis ($\rho=-0.41$,

$P=0.002$), baseline GH ($\rho=0.39$; $P=0.003$) and IGF-I levels ($\rho=0.28$; $P=0.039$), baseline tumor volume ($\rho=0.37$; $P=0.005$), final GH ($\rho=0.77$; $P<0.0001$) and IGF-I levels ($\rho=0.72$; $P<0.0001$), percent IGF-I suppression ($\rho=0.42$; $P=0.001$), final tumor volume ($\rho=0.52$; $P<0.0001$), and percent tumor shrinkage ($\rho=-0.52$; $P<0.0001$). The final dose was also correlated with the percent increase of glucose ($\rho=0.34$; $P=0.01$) and decrease of insulin levels ($\rho=0.31$; $P=0.021$).

The final dose was predicted by patients' age at diagnosis ($t=-2.2$; $P=0.032$) and baseline tumor volume ($t=2.1$; $P=0.043$).

Discussion

The results of the present study show that increasing LAR doses of up to 40 mg/q28d induces a further decrease of GH and IGF-I levels and tumor shrinkage in patients resistant to 30 mg at the same injections interval, thus inducing disease control in 25% of them. The patients requiring such high doses are younger, have higher GH levels and bigger tumors at diagnosis than those who achieve disease control with lower doses. Overall, only a minority of patients with normal glucose tolerance at diagnosis impaired their glucose tolerance at the end of the 24-month treatment; increased dose up to 40 mg/q28d did not worsen glucose tolerance more than a dose of 20 mg/q28d.

The primary objective of therapy in acromegaly is to reverse symptoms and signs of the disease, treat the underlying cause, prevent disease recurrence, and improve long-term survival (16). It is presently accepted that achieving GH levels of $<2 \mu\text{g/l}$ is associated with near-normal life expectancy (1). Surgery via the transsphenoidal route with or without adjuvant radiotherapy is still considered the treatment of choice, but even despite recent advances the overall surgical cure rate remains around 50% and radiotherapy may take 5–10 years to lower GH to safe levels (17). Radiotherapy has the additional disadvantage of inducing a high incidence of hypopituitarism, which itself is associated with excess mortality (18, 19). These concerns have led to a reappraisal of somatostatin analogs therapy for acromegaly, not just as an adjunct to surgery and radiotherapy, but for using as first-line primary therapy (20).

In this setting, Octreotide-LAR is efficacious in the medical approach to acromegaly. As shown in a recent meta-analysis (2), control of GH and IGF-I secretions is reported in 57 and 67% respectively, after Octreotide-LAR therapy with similar efficacy with respect to GH levels and only marginally greater IGF-I normalization when adjunctive therapy was compared with first-line. In the present study, we confirm that first-line Octreotide-LAR therapy for 12 months (a period of

treatment similar to that reported in the meta-analysis (2)) induced control of GH and IGF-I levels in 55.3 and 44.6% respectively. Cure rate increased up to 80.3% with continuous treatment for 24 months and up-titration of the drug dose to 40 mg/q28d. However, if we include in the calculation of treatment efficacy the 16 patients who were withdrawn from treatment prior to 24 months, the overall disease control decreased to 62.5%, still remaining higher than that observed at 12 months.

The advantage of up-titration of the dose of Octreotide-LAR has been poorly investigated; besides the evidence that higher doses are associated with worse responsiveness (2), some further benefit in suppressing GH and IGF-I levels by increasing the dose from 20 to 30 mg/q28d had been reported (7–9, 21, 22). Of the 32 patients requiring an increase of the dose from 20 to 30 mg/q28d after the initial 3 months of treatment, 15 achieved disease control within 12 months and another six in the second 12 months after further increase of the dose to 40 mg/q28d. These data are in line with those recently reported by Cozzi *et al.* (8) and Ayuk *et al.* (23), who reported a very high success rate (67–70% of cases) after prolonged Octreotide-LAR treatment given first-line or adjunctive therapy with a maximal dose of 30 mg/q28d. Apparently, the prevalence of disease control in the present study and in the previous ones (8, 23) is not different; however, treatment duration lasted 48 months in the former and 41 months in the latter (that also included patients treated as second-line). Thus, one implication of the results reported in the present study is that increase of the dose could shorten the period required for GH and IGF-I control.

However, the analytical collection of the data in the present study allowed us also to show that some further suppressive effect is obtained in patients maintaining the same dose during the study also. In fact, in the 24 patients of Group A, who received the same dose of 20 mg/q28d for 24 months (four of them indeed decreased the dose to 10 mg after 12 months but were considered together with the other patients), we observed a further suppression both of GH and IGF-I levels (by a median of 32.7 and 15.4% respectively) during the second 12 months of treatment. Further hormone suppression was obtained even if all patients achieved control of GH and IGF-I levels during the first 12 months of treatment. Another clinically important observation is that increase of the dose from 30 to 40 mg/q28d after 12 months of treatment in 17 patients was accompanied by control of GH and IGF-I levels in six patients and by an overall median GH suppression of 65.4% and IGF-I suppression of 29.6%. The dose of 40 mg/q28d induced a success rate that can be considered little since only six out of 17 patients achieved disease control in the 12 months of treatment. However, the increment of the dose further decreased significantly both GH and IGF-I levels thus suggesting

that prolonged treatment at the same high dose could increase the success rate of the treatment in a shorter period of time, as mentioned previously. In fact, since further suppression of GH and IGF-I levels during the second year of treatment (by 40.9 and 28.1% respectively) was also found in the patients who maintained a dose of 30 mg/28d, out of the six patients achieving disease control with the dose increment to 40 mg/q28d only three would have achieved the same effect maintaining the 30 mg dose. The availability of GH-receptor antagonist in the recent years has provided another efficacious tool to control IGF-I excess in 75–100% of resistant patients with acromegaly (24–26). This suggests that prolonging Octreotide-LAR up to 40 mg could not be anymore necessary in resistant patients. However, increase in tumor size can be experienced by patients with large tumors that did shrink during somatostatin analogs therapy (26); some increase in liver function tests is also reported during GH-receptor antagonist treatment (27).

Shrinkage of tumor mass by ~50% is reported in patients with acromegaly treated with somatostatin analogs given first-line (4, 5). In a recent prospective study, we reported tumor shrinkage >25% in 75.5% and >50% in 44.4% of 99 patients after 12 months of treatment with somatostatin analogs (6). In the present study, we showed that increasing the drug dose up to 40/q28d induced further tumor shrinkage when compared with the lower dose. We also showed that prolonged treatment for 24 months in the entire series induced a greater tumor shrinking effect than a 12-month treatment, and that patients treated with the same dose from 6 to 24 months achieved further tumor shrinkage. These results suggest that in patients partially responsive to Octreotide-LAR increasing the drug dose and prolonging the period of treatment induce greater tumor shrinkage than in the first period of treatment with a lower dose. This also demonstrates that the observation reported in the meta-analysis by Freda *et al.* (2) showing that increasing the number of months of therapy beyond 6 months was not associated with an increased likelihood of tumor shrinkage was not entirely appropriate but was essentially drawn from data originated by short-term treatments reported in the majority of the studies.

The most important shortcoming of prolonged somatostatin analogs treatment is the impairment of glucose tolerance. Although most studies have shown no significant effect on glucose tolerance, some groups reported raised glucose or glycosylated hemoglobin levels after 6 months of treatment (28, 29). In our study, the overall glucose tolerance did not change, but 25% of patients with normal glucose tolerance at baseline developed IGT, and 10% with IGT developed overt diabetes. Besides, 20% of patients with IGT normalized their glucose tolerance and 28.3% of those with diabetes did not require glucose-lowering drugs

anymore during Octreotide-LAR treatment. To note this, the dose of different treatments for diabetes was increased in five out of the 12 diabetic patients (41.7%) at diagnosis. In all patients, insulin sensitivity improved but β -cell function was reduced. Even if these results are reassuring, it should be reminded that treatment with GH-antagonist specifically improves glucose tolerance (30). Thus, in patients with diabetes, first-line treatment with somatostatin analogs should balance tumor size reduction with a possible worsening of glucose tolerance that requires an increase in the doses of glucose-lowering drugs in almost half of the patients.

Generally, the treatment with Octreotide-LAR, even at high doses, is very well tolerated as also shown in the present study. New gallstone formation has been reported in $\sim 24\%$ of patients treated with depot somatostatin analogs (31), as confirmed in this study (25.3%). Abdominal discomfort is common at treatment beginning and generally subsides spontaneously without any specific treatment except in a minority of cases (21.1% of the present series).

Some studies are reporting on the beneficial effects of combination schemes of treatment including somatostatin analogs plus dopamine-agonists (32) or once weekly GH-antagonist (33). Both GH-antagonist and dopamine-agonists have some limitations since they induce side effects, and have never been reported to induce further tumor shrinkage. Thus, even if increase of the dose of LAR up to 40 mg/q28d might have similar efficacy of other treatment schemes, we suggest that it would target hormone excess and tumor shrinkage in the same time with no evidence of worsening of known side effects.

Conclusion

The results of the present study show that increase of Octreotide-LAR dose up to 40 mg/q28d in patients resistant to the 30 mg dose is followed by greater suppression of GH and IGF-I levels and induces greater tumor shrinkage without further impairment of glucose tolerance when compared with lower doses. Besides, we demonstrated that patients treated for 24 months at the same dose had further tumor shrinkage when compared with 12-month follow-up. Altogether, these results suggest that a new dosage schedule is applied in patients with acromegaly treated first-line with Octreotide-LAR by starting with a 30 mg/q28d and down- or up-titrated to 20 or 40 mg in accordance with individual patient's response of GH and IGF-I levels. We also support modern acromegaly treatment guidelines indicating that prolonged treatment is performed in patients bearing large tumors that do not require immediate surgical debulking because of neurological deficits.

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