Efficacy and Safety of the New 60-mg Formulation of the Long-Acting Somatostatin Analog Lanreotide in the Treatment of Acromegaly

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Recently, a new slow-release (SR) formulation of lanreotide (LAN) comprising 60 mg of the drug incorporated in microspheres of biodegradable polymers (SR-LAN 60) has become available. The aim of our study was to assess the effectiveness of SR-LAN 60, administered every 21 to 28 days, as well as its tolerability in the long-term treatment of acromegalic patients treated with SR-LAN 30. Twenty patients with acromegaly (10 males and 10 females) were enrolled in this open study. Thirteen patients had undergone surgery, but with incomplete resection of the pituitary tumor. All patients, treated with intramuscular (IM) SR-LAN 30 injections every 10 days for 12 to 24 months, started SR-LAN 60 (Ipsen-Beaufour, Milan, Italy) administration 10 days after the last injection of SR-LAN 30. Growth hormone (GH) levels were determined on the day of the first injection of SR-LAN 60, and 10, 20, and 30 days after. According to the GH levels reached on day 30, patients received SR-LAN 60 every 28 days if GH levels were below 2.5 μg/L (group A) and every 21 days if GH levels were above 2.5 μg/L (group B). In group A, after the 8th month, SR-LAN 60 treatment resulted in well-controlled GH levels in 9 of 10 patients in comparison to SR-LAN 30 treatment every 10 days (6 of 10 patients). Normal age-adjusted insulin-like growth factor-I (IGF-I) levels were achieved in 4 of 10 patients, as in treatment with SR-LAN 30. In group B, SR-LAN 60 treatment resulted in well-controlled GH levels in 4 of 10 patients, as in treatment with SR-LAN 30 every 10 days. Normal age-adjusted IGF-I levels were achieved in 3 of 10 patients after SR-LAN 60 in comparison to SR-LAN 30 treatment every 10 days (1 of 10 patients). During SR-LAN 60 therapy, an improvement was also observed in signs and symptoms of active acromegaly and no relevant side effects were detected. In conclusion, this study shows that SR-LAN 60 treatment is able to induce a good control of circulating GH and IGF-I levels in most acromegalic patients. The first injections of SR-LAN 60 are very helpful in predicting the optimal long-term injection frequency. Patients on SR-LAN 30 can be safely and effectively shifted to SR-LAN 60.

ACROMEGALY is a clinical condition, due to excessive chronic growth hormone (GH) and insulin-like growth factor-I (IGF-I) secretion, and is almost invariably caused by a somatotrophic adenoma and associated with increased mortality and morbidity from cardiovascular, cerebrovascular, and neoplastic disease.[1,2] The aim of therapy for acromegaly is to remove the source of GH hypersecretion, normalize the GH/IGF-I axis hyperactivity and the related morbidity, and increase life expectancy to that of the general population.[3,4]

The modalities of treatment of GH-secreting pituitary adenomas include surgical removal and/or radiotherapy and pharmacological agents such as dopamine agonists and long-acting somatostatin analogs.[5-9] Surgery is the most rapid way to reduce GH and IGF-I levels. However, up to 50% of acromegalic patients are not cured by neurosurgery alone.[10] Radiotherapy, both conventional and stereotactic, is effective in treating acromegaly, but the process is slow and hypopituitarism can occur in as many as 50% of patients.[11,12] Medical therapy with the long-acting analogs of somatostatin (octreotide [OCT] and lanreotide [LAN]) is now an attractive option both for combination treatment and as a first line treatment of acromegaly. Subcutaneous OCT, administered in 3 daily injections, was the first widely used short-acting somatostatin analog. Recently, long-acting depot formulations have become available, such as OCT long-acting release (OCT-LAR) and slow-release lanreotide (SR-LAN), that seem likely to offer significant advantages in terms of drug efficacy, tolerability, and patient compliance.

In long-term treatment, the first formulation of lanreotide (SR-LAN 30 mg), imtramuscularly (IM) injected 2 to 3 times per month, has been shown to reduce GH concentrations to less than 2.5 μg/L and normalize IGF-I levels in up to 64% of patients with active acromegaly.[13-15]

Other investigators have shown that long-term treatment with OCT-LAR at 28-day intervals lowers GH levels to below 2 μg/L in 56% and normalizes IGF-I levels in 66% to 88% of patients.[16,17]

Recently, a new SR formulation of LAN comprising 60 mg of the drug incorporated in microspheres of biodegradable polymers (SR-LAN 60) has become available.[18] The aim of the present study was to assess the effectiveness of SR-LAN 60, administered every 21 to 28 days, as well as its tolerability in the long-term treatment of acromegalic patients treated with SR-LAN 30.

PATIENTS AND METHODS

Patients

Twenty patients with acromegaly, 10 men and 10 women (aged 35 to 77 years; median, 59.5), were enrolled in this open study, performed at the University of Brescia, Ferrara, Padua, and Rome after providing

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Submitted June 1, 2001; accepted September 3, 2001.

Supported by grants from the Italian Ministry of University and Scientific and Technological Research (40%, Project 9906153187-004, 1999 and 60% 2000) Ipsen, S.P.A. (Milan, Italy), and the Associazione Ferrarese dell'Ipertensione Arteriosa.

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0026-0495/02/5103-0016$35.00/0

doi:10.1053/meta.2002.30526

Table 1. Characteristics of Acromegalic Patients

Patients	Sex	Age (yr)	Disease Duration (yr)	Adenoma	Treatment Before LAN-SR 30	CT/MRI
Group A						
1	M	35	20	*M*	TSA + OCT	R
2	F	56	18	*M*	TSA + OCT	R
3	M	62	11	*M*	TSA + OCT	R
4	F	70	15	*M*	TSA + RT + OCT	R
5	M	47	10	*m*	TSA + OCT	R
6	M	62	12	*M*	TSA + OCT	R
7	M	60	12	*M*	TSA + OCT	R
8	F	75	19	*m*	OCT	EM
9	M	52	15	*m*	OCT	EM
10	M	52	5	*m*	None	IM
Group B						
11	M	73	30	*m*	OCT	EM
12	F	61	10	*m + es*	None	EM + es
13	M	64	11	*M*	TSA	R
14	M	51	8	*M*	TSA + OCT	R
15	F	59	6	*m*	TSA + OCT	R
16	F	40	8	*M*	TSA + RT + OCT	R
17	F	37	6	*M*	TSA + OCT	R
18	F	77	10	*m*	None	EM
19	F	75	15	*m*	None	EM
20	F	46	13	*M*	TSA + RT + OCT	R

Abbreviations: M, male; F, female. *m,* microadenoma; *M,* macroadenoma; *es,* empty sella; TSA, transsphenoidal adenomectomia; RT, radiotherapy; OCT, octreotide; IM, intrasellar microadenoma; EM, extrasellar microadenoma; R, remnant of adenoma.

written informed consent, approved by the local ethical committees. Patient characteristics and clinical data are reported in Table 1.

Diagnosis of acromegaly was assessed according to clinical profile and biochemical data (high GH plasma levels not suppressible by oral glucose load to < 1 ng/mL, and elevated age-matched IGF-I concentrations). Disease duration (12.7 $\pm$ 6.5 years, mean $\pm$ SD) was assessed by patient interview, comparison of photographs taken in the last 2 decades, and dating the onset of acral enlargement.

At diagnosis 11 patients had macroadenomas, 8 microadenomas, and 1 an empty sella with evidence of a microadenoma invading the cavernous sinus. Eleven macroadenoma and 2 microadenoma patients had undergone surgery, but with incomplete resection of the pituitary tumor, and evidence of parasellar or intrasellar residual mass at post-surgery pituitary magnetic resonance imaging (MRI). Immunohistochemical diagnosis had shown a GH secreting adenoma in 11 patients and a GH-prolactin–secreting adenoma in 2 patients. Surgery was followed by radiotherapy in 3 patients, at least 5 years before this study. Pituitary hormone deficiency, replaced with L-T4 therapy in 2 patients and with sexual steroids in other 2, was clinically and biochemically amended.

All patients had been treated with SR-LAN 30 for 12 to 24 months before the study and 4 had received it as primary therapy. Fifteen patients had previously been treated with subcutaneous OCT, 3 of whom received it as primary therapy. Seven microadenoma patients had not been treated with either surgery or radiotherapy. None of the patients was receiving dopamine agonist therapy.

Four acromegalic patients had diabetes mellitus (disease duration, 2.5 $\pm$ 1.3 years), treated with oral hypoglycemic drugs, and 6 patients had hypertension which was well controlled by initial treatment. Three patients had undergone cholecystectomy for gallbladder stones 2 to 4 years before the study, 2 of them during OCT treatment and 1 during SR-LAN 30.

Study Protocol

All patients, on chronic SR-LAN 30 (Ipsen-Beaufour, Milan, Italy) IM injections every 10 days started SR-LAN 60 mg (Ipsen-Beaufour) administration 10 days after the last injection of SR-LAN 30. Blood samples for GH determination were drawn on the day of the first injection of SR-LAN 60, and 10, 20, and 30 days after.

According to the GH levels reached on day 30 after SR-LAN 60 administration, patients were divided into 2 groups (Fig 1): (1) patients with GH levels below 2.5 μg/L, who received an IM injection of SR-LAN 60 every 28 days for 8 months (group A); and (2) patients with GH levels above 2.5 μg/L, who received an IM injection of SR-LAN 60 every 21 days for 8 months (group B).

In all patients, before every injection of SR-LAN 60, 2 blood samples were collected at 15-minute intervals in the morning after an overnight fast and rest while the patients were awake and in a supine position with an indwelling needle inserted into an antecubital vein and kept open with a slow infusion of saline. IGF-I was measured in a single sample. Biochemical evaluation, including fasting blood glucose and amylase concentrations, and liver function parameters, was performed before each SR-LAN 60 injection. Glycosylated hemoglobin (HbA_{1c}) was evaluated before and every 2 months during SR-LAN 60 treatment.

Visual field, examined by Goldmann-Friedmann perimetry, and gallbladder ultrasound were performed before and 8 months after SR-LAN 60 treatment.

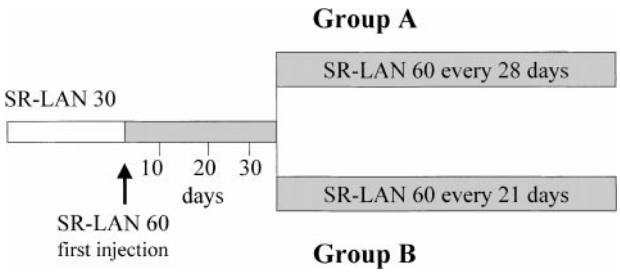

Fig 1. Study flow chart.

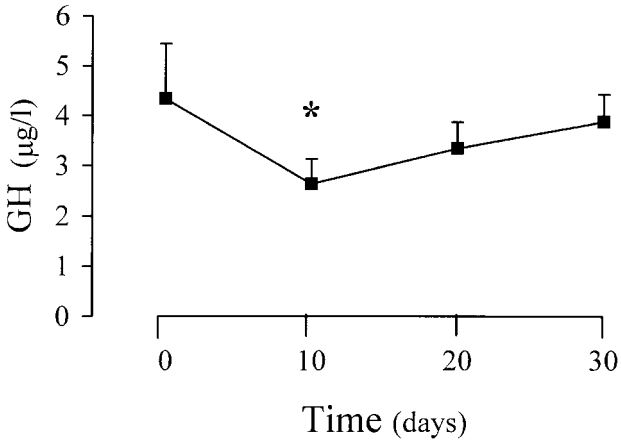

Fig 2. Plasma GH levels (mean ± SEM) in 20 acromegalic patients on the day of the first injection of SR-LAN 60 (0) and 10, 20, and 30 days after. *$P < .05$ *v* day 0.

MRI of pituitary was performed before and after 8 months of SR-LAN 60 therapy. MRI (1.0 Tesla, 1.0 T General Electric, Signa) was used to assess T1-weighted sequences and 3-mm slices in sagittal and coronal sections, before and after intravenous injection of gadolinium chelate.

Biochemically, acromegaly was considered controlled when baseline GH plasma concentration was below 2.5 μg/L in fasting samples, with normal IGF-I levels for age.[19]

Before and during SR-LAN 60 treatment, headache, hyperhydrosis, arthralgia, and paresthesia were scored at each visit (every 21 or 28 days) as absent (0), mild (1), moderate (2), or severe (3).

Assays

Plasma GH was measured by immunoradiometric assay with reagents supplied by Nichols Institute Diagnostics (San Juan Capistrano, CA). The detection limit was 0.05 μg/L, with intra- and interassay coefficients of variation of 3.3% and 6.1%, respectively.

Plasma IGF-I was determined by radioimmunoassay (RIA) using a commercially available Kit (Medgenix Diagnostic S.A, Fleurus, Belgium), after acid-ethanol extraction from ethylenediamine tetraacetic acid–treated plasma. The intra- and interassay coefficients of variation were 9.6% and 6.1%, respectively. In our laboratories, age-adjusted normal ranges for IGF-I levels were 131 to 483 ng/mL (age 20 to 30 years), 120 to 397 ng/mL (31 to 40 years), 113 to 306 ng/mL (41 to 50 years), 100 to 250 ng/mL (51 to 60 years), and 92 to 229 ng/mL (60 to 70 years).

All blood samples from an individual were run in the same assay and in duplicates. Glucose, HbA_{1c}, amylase, and other biochemical parameters were measured by standard methods.

Statistical Analysis

Statistical evaluation of the data was performed using paired Student's *t* test and analysis of variance (ANOVA) as applicable. *P* values less than .05 were considered significant. Results are expressed as the mean ± SEM.

RESULTS

The First Injection of SR-LAN 60: Effect on GH Levels

Ten days after the last injection of SR-LAN 30, the mean GH and IGF-I levels of the patients were 4.34 ± 1.11 μg/L (range, 0.80 to 15; median, 2.75 μg/L) and 376.70 ± 44.48 ng/mL (range, 185 to 1,074; median, 370.50 ng/mL), respectively (Fig 2).

Ten days after the first injection of SR-LAN 60, the mean GH level was 2.64 ± 0.50 μg/L (range, 0.40 to 4.75; median, 1.82 μg/L), with a significant ($P < .05$) reduction (>50% in 7 of 20 patients) as compared to that observed 10 days after the last SR-LAN 30 injection (Fig 2).

On days 20 and 30 after the injection of SR-LAN 60, the mean GH levels were 3.35 ± 0.53 μg/L (range, 0.70 to 8; median, 2.72 μg/L) and 3.89 ± 0.55 μg/L (range, 0.90 to 8; median, 3.90 μg/L), not significantly different from the GH concentration detected 10 days after the last SR-LAN 30 injection (Fig 2).

After the first SR-LAN 60 injection, plasma GH concentration fell to below 2.5 μg/L in 15 of 20 patients on day 10. Among these patients only in 10 did GH levels persist below 2.5 μg/L at 20 and 30 days.

28-Day Interval SR-LAN 60 Regimen: Effects on GH/IGF-I Levels (group A)

Patients with GH levels below 2.5 μg/L on day 30 after the first SR-LAN 60 injection were submitted to a 28-day interval with SR-LAN 60 regimen. GH and IGF-I levels in these patients are shown in Fig 3.

GH levels decreased to 1.98±0.38 μg/L (range, 0.60 to 4.40; median, 1.88 μg/L), after a 2-month treatment and remained well controlled during treatment: 1.68 ± 0.57 μg/L (range, 0.90 to 2.50; median, 1.80 μg/L) after the 8th month in comparison with GH levels obtained during SR-LAN 30 treatment (2.61 ± 0.72 μg/L; range, 0.80 to 8; median, 1.95 μg/L) (Fig 3).

In this group of patients (A), after the 8th month, SR-LAN 60 treatment every 28 days resulted in well-controlled GH levels in 9 of 10 patients in comparison to SR-LAN 30 treatment every 10 days (6 of 10 patients).

IGF-I levels were 323.50 ± 45.59 ng/mL (range, 54 to 531; median, 343 ng/mL), after a 2-month treatment and remained unchanged after the 8th month: 317.70 ± 31.22 ng/mL (range, 102 to 460; median, 325 ng/mL), showing no difference with IGF-I levels obtained during SR-LAN 30 treatment (mean, 303.10 ± 38.01; range, 111 to 483; median, 291 ng/mL) (Fig 3).

Normal age-adjusted IGF-I levels were achieved in 4 of 10 patients, as in treatment with SR-LAN 30.

21-Day Interval SR-LAN 60 Regimen: Effects on GH/IGF-I Levels (group B)

Patients with GH levels above 2.5 μg/L at day 30 after the first SR-LAN 60 injection were submitted to a 21-day interval SR-LAN 60 regimen. GH and IGF-I levels in these patients are shown in Fig 4.

GH levels decreased to 3.59±0.64 μg/L (range, 0.90 to 6.25; median, 4.15 μg/L) after a 2-month treatment, and remained well controlled during treatment: 3.73 ± 0.77 μg/L (range, 0.80 to 6.45; median, 3.55 μg/L) after the 8th month, in

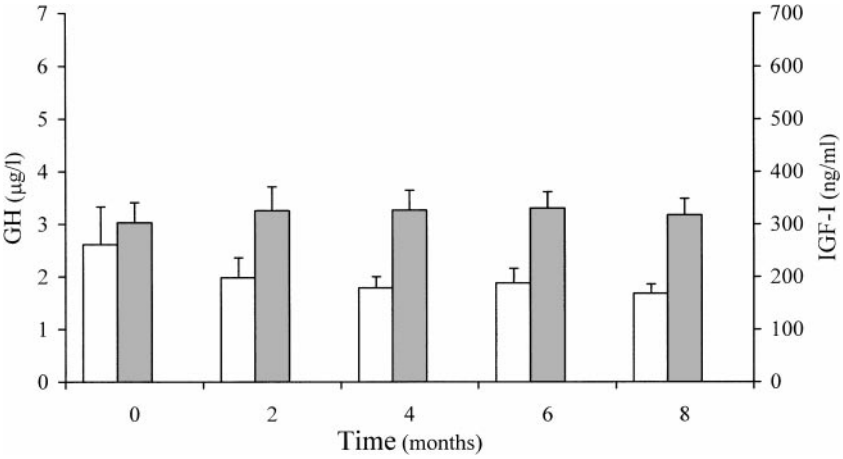

Fig 3. Plasma GH (white column) and IGF-I (grey column) levels (mean ± SEM) in 10 acromegalic patients before (0) and during SR-LAN 60 administered every 28 days.

comparison to GH levels obtained during SR-LAN 30 treatment (5.27 ± 1.48 μg/L; range, 0.90 to 15; median, 4.08 μg/L) (Fig 4).

In this group (B), SR-LAN 60 treatment every 21 days resulted in well-controlled GH levels in 4 of 10 patients as in treatment with SR-LAN 30 every 10 days.

IGF-I levels were 520 ± 104.88 ng/mL (range, 100 to 1,200; median, 361.50 ng/mL) after a 2-month treatment and decreased during treatment: 395.50 ± 84.44 ng/mL (range, 95 to 994; median, 325 ng/mL) after the 8th month, in comparison to IGF-I levels obtained during SR-LAN 30 treatment (mean, 450.30 ± 75.53; range, 176 to 1,074; median, 411 ng/mL) (Fig 4).

Normal age-adjusted IGF-I levels were achieved in 3 of 10 patients after SR-LAN 60 in comparison with SR-LAN 30 treatment every 10 days (1 of 10 patients).

Effects on Symptoms of Acromegaly

Before SR-LAN 60 treatment, headache, hyperhydrosis, arthralgia, and paresthesia were present in 5 (25%), 6 (30%), 9 (45%), and 4 (20%) patients, respectively. These symptoms significantly improved in the most patients after 4 months of SR-LAN 60 therapy (Table 2). Headache disappeared in 3 patients and decreased in 2 patients. Hyperhydrosis disappeared in 3 patients, decreased in 2, and remained unchanged in 1. Arthralgia disappeared in 4 patients, improved in 4, and remained unchanged in 1. Paresthesia disappeared in 3 patients, decreased in 2, and remained unchanged in 1.

During SR-LAN 60 therapy, no changes in visual field were observed in any patients. No significant change in the size of tumor masses or remnants was found at MRI after SR-LAN 60 therapy.

Tolerability

Tolerability was excellent in all cases. No patient was withdrawn from SR-LAN 60 therapy because of side effects.

Nine patients reported mild pain in the injection site, which disappeared 1 to 2 days after the injections. Abdominal discomfort was referred by 7 patients and steatorrhea by 3 patients for 1 to 4 days after the first injection of SR-LAN 60, and spontaneously disappeared without specific treatment. Symptoms were similar to those observed during SR-LAN 30 treatment.

In nondiabetic acromegalic patients, the mean fasting glucose levels did not significantly change during SR-LAN 60 treatment, at 28- or 21-day intervals, as compared to SR-LAN 30 (group A, 103.44 ± 3.22 mg/dL at 8 months of treatment *v*

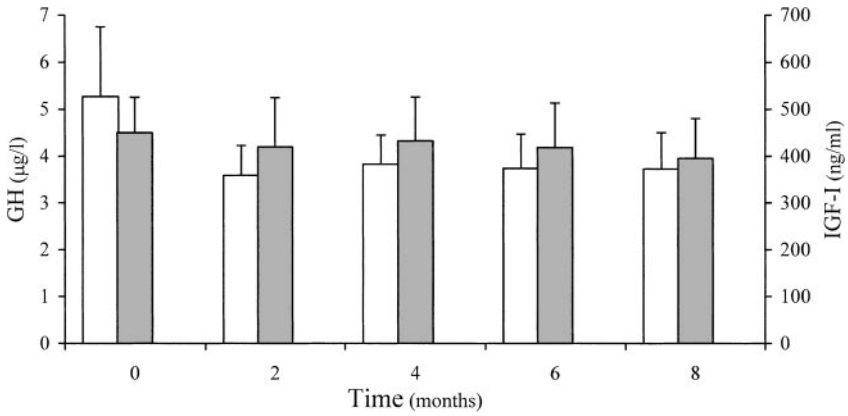

Fig 4. Plasma GH (white column) and IGF-I (grey column) levels (mean ± SEM) in 10 acromegalic patients before (0) and during SR-LAN 60 administered every 21 days.

Table 2. Effects of SR-LAN 30 and SR-LAN 60 Treatment on Symptoms of 20 Acromegalic Patients

Symptom	SR-LAN 30	2 Months	4 Months	6 Months	8 Months
Headache	0.82 ± 0.29	0.3 ± 0.15	0.21 ± 0.13*	0.21 ± 0.13*	0.21 ± 0.13*
Arthralgia	1.41 ± 0.26	0.9 ± 0.23	0.58 ± 0.21†	0.58 ± 0.22†	0.58 ± 0.22†
Hyperhidrosis	0.81 ± 0.15	0.5 ± 0.96	0.31 ± 0.95*	0.31 ± 0.95*	0.31 ± 0.95*
Paraesthesia	0.91 ± 0.23	0.5 ± 0.16	0.29 ± 0.15†	0.29 ± 0.15†	0.29 ± 0.15†

NOTE. The mean ± SE symptom scores are shown at baseline and during SR-LAR 60 treatment, where 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

Significance values are shown as *$P < .05$, †$P < .02$.

99.55 ± 3.79 mg/dL; group B, 103.71 ± 4.44 mg/dL at 8 months *v* 109.60 ± 5.96 mg/dL).

In those patients, the mean HbA_{1c} levels did not significantly change during SR-LAN 60 treatment as compared to SR-LAN 30 (group A, 5.13% ± 0.17% at 8 months of treatment *v* 5.48% ± 0.29%; group B, 5.67% ± 0.40% at 8 months *v* 5.57% ± 0.32%).

Two of 4 patients with diabetes mellitus showed a striking reduction in fasting glucose (from 280 to 130 mg/dL and from 160 to 125 mg/dL, respectively) and HbA_{1c} levels (from 11.50% to 6.70% and from 10% to 7%, respectively) in comparison to SR-LAN 30 treatment, whereas no significant change in fasting glucose and HbA_{1c} levels was detected in the other 2.

In no patients were there changes in other biochemical parameters during SR-LAN 60 treatment, at 28- or 21-day intervals, as compared to SR-LAN 30 therapy.

No new gallstones occurred during SR-LAN 60 treatment. Blood pressure levels were not significantly changed during SR-LAN 60 versus SR-LAN 30. No changes in hypothesive therapy were required during SR-LAN 60 treatment in hypertensive patients.

DISCUSSION

The therapeutic goal of acromegaly is to improve long-term survival and clinical conditions of the patients, by removing tumor mass and normalizing GH and IGF-I levels.[4] The use of somatostatin analogs has proven to be effective in controlling GH and IGF-I excess in active acromegaly.[20-22] The development of long-acting formulations (OCT-LAR and SR-LAN) has overcome the inconvenience of a scarce compliance for multiple daily injections.[16,23]

Recently, a new formulation of lanreotide, SR-LAN 60 mg, administered every 21 to 28 days has become clinically available. To our knowledge, data about the effect of SR-LAN 60 treatment for acromegaly are currently scant.[18,24]

The first data on SR-LAN 60 have shown that this new formulation can effectively reduce GH secretion in de novo patients, and compared to previous treatment with SR-LAN 30, it is able to maintain safe GH levels with less frequent injections.[18,24]

The aim of our study was to evaluate the effectiveness of this new formulation of lanreotide as well as its tolerability in the long-term treatment of acromegalic patients previously treated with SR-LAN 30. Our data demonstrated that SR-LAN 60 is able to reduce GH levels to below 2.5 μg/L in 65% of the patients, and to normalize IGF-I levels in 35% of cases, thus obtaining a better overall control of hormonal concentrations as compared to SR-LAN 30. In fact, even if the mean values during SR-LAN 60 and SR-LAN 30 did not significantly differ, the previous SR-LAN 30 treatment had induced a GH suppression only in 50% of the patients and IGF-I normalization only in 20%.

At the end of the 8th month, SR-LAN 60 treatment reduced GH levels to below 2.5 μg/L in 13 patients (65%), between 2.5 to 5 μg/L in 4 patients (20%), and above 5 μg/L in 3 patients (15%). IGF-I levels were normalized in 7 of 20 patients (35%).

During SR-LAN 60 therapy, an improvement was also observed in signs and symptoms of active acromegaly. Most patients showed a reduction in headache, hyperhydrosis, and arthralgia, and 35% of patients had become asymptomatic, probably due to the more prolonged GH suppressive effect of SR-LAN 60 as compared to SR-LAN 30.

Our data show that almost half of the acromegalic patients (9 of 20) were well controlled by a treatment schedule with SR-LAN 60 injections every 28 days, whereas the other 4 patients benefited from SR-LAN 60 injections every 21 days. These results suggest that SR-LAN 60 may be more effective than SR-LAN 30, even if the interval between drug injections is lengthened.

Careful monitoring of GH levels after the first SR-LAN 60 injection can define the most suitable schedule of treatment for controlling GH secretion. In fact, patients who showed a GH value below 2.5 μg/L, 30 days after the first injection, were almost invariably well controlled by the same treatment schedule in the long term. In contrast, almost half of the patients that did not achieve GH levels below 2.5 μg/L 30 days after the first SR-LAN 60 injection were below this biochemical target after 8 months' treatment with SR-LAN 60 injections every 21 days. It should be noted that a number of uncontrolled patients may improve their response to SR-LAN 60 by decreasing the interval of injections to below 21 days. Moreover, stable GH values were observed in our patients after the 3rd injection of SR-LAN 60, indicating that only after a 2- to 3-month period of treatment should a decision be made regarding increasing the injection frequency.

In previous studies, the response to SR-LAN 30 therapy was not influenced by previous surgical treatment and/or radiotherapy.[15] Our data show that 7 microadenoma patients treated with medical therapy alone were less responsive to SR-LAN as compared to patients previously treated with surgery. In fact, only 1 of the patients who did not undergo surgery or radio-

therapy achieved GH levels less than 2.5 μg/L with normalization of IGF-I levels, whereas the other 6 had GH levels between 2.5 and 5 μg/L with IGF-I normalization in 1 case, both during SR-LAN 30 and SR-LAN 60 treatment. These data indicate that other factors, such as the interindividual difference in intrinsic sensitivity to somatostatin analogs[25] or higher baseline secretion rate from the adenomatous tissue, could account for the unsatisfactory control of disease in these patients during SR-LAN therapy.

The present data do not allow us to compare the efficacy of SR- LAN 60 with the other monthly administered somatostatin analog, OCT-LAR. In our study, although normal GH levels were obtained in a large percentage of patients, a reduction in IGF-I levels was obtained in fewer patients. This confirms the greater efficacy of OCT-LAR versus SR-LAN 60 in normalizing IGF-I levels, as has already been reported in the comparative studies with SR-LAN 30.[16,27-29] After SR-LAN 60 therapy, no significant change in tumor size or residual mass was observed in the patients.

No relevant side effects were detected during SR-LAN 60 treatment. None of the patients had significant changes in the tendency to gallstone and biliary sludge formation, nor did they display pancreatitis, unlike other studies in which long-term treatment with SR-LAN 30 induced occurrence of new gallstones or acute pancreatitis. This suggests that SR-LAN 60 may reduce the prevalence of major gastrointestinal side effects.[21,30]

Transient gastrointestinal symptoms (abdominal discomfort and steatorrhea), when reported, disappeared after the 3rd injection. Pain, erythema, and swelling at the injection site were milder and transient as compared to SR-LAN 30. Moreover, monthly injections apparently increased patient compliance to treatment compared to the 10 day schedule, suggesting that this drug may improve the quality of life.

No significant changes were observed in blood pressure either in normotensive or hypertensive patients, as reported previously with SR-LAN 30 therapy.[21]

In nondiabetic acromegalic patients, SR-LAN 60 did not cause changes in carbohydrate metabolism. In patients with diabetes mellitus, beneficial effects were seen in fasting glucose levels and HbA_{1c} percentage in 2 of 4 patients, with a stable control of these parameters in the remaining two patients. Although mild deterioration in carbohydrate metabolism was occasionally reported with SR-LAN 30,[21] our data indicate that SR-LAN does not worsen diabetes in the acromegalic patients.

In conclusion, this study shows that: (1) SR-LAN 60 treatment is able to induce a good control of circulating GH and IGF-I levels in most acromegalic patients, particularly in those previously treated with neurosurgery (regardless of pretreatment GH levels). Our results further indicate that administration of SR-LAN 60 every 28 days is able to control GH secretion in about half of the acromegalic patients and the shortening of the injection interval to 21 days may improve the number of well-controlled patients (2) A 1-month period with GH sampling every 10 days, after the first injection of SR-LAN 60, is very helpful in the prediction the optimal long-term injection frequency; and (3) patients on SR-LAN 30 can be safely and effectively shifted to SR-LAN 60, and after the 3rd SR-LAN 60 injection a further adjustment of the analog dose could be performed.

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