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Two-Year Follow-Up of Acromegalic Patients Treated with Slow Release Lanreotide (30 mg)*

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ABSTRACT

Pharmacotherapy of acromegaly has been improved in recent years as new long-acting somatostatin analogs have became available; they have been suggested as an alternative treatment to pituitary surgery and radiotherapy. To avoid the inconvenience of multiple daily injections during long-term therapy, a slow release formulation of lanreotide (LAN), to be administered im at a dose of 30 mg every 7–14 days, has been introduced in the therapeutic management. The suppressive effects of a short-term LAN treatment on GH and insulin-like growth factor I (IGF-I) hypersecretion were shown to be similar to those obtained with sc octreotide. However, scant data have been reported concerning a long-term treatment with this drug. In the present study the efficacy and tolerability of a 24-month LAN treatment were evaluated in 118 active acromegalic patients; 71 had been previously operated on and treated with sc octreotide (operated patients), 24 previously operated on had been irradiated and treated with sc octreotide (irradiated patients), and the remaining 23 were newly diagnosed (*de novo* patients). The efficacy was considered on the basis of controlled GH (fasting, <7.5 mU/L; glucose-suppressed, <3.0 mU/L) and IGF-I (age-adjusted normal values) secretion. In the 118 patients as a whole, circulating GH and IGF-I levels were significantly decreased during the 24-month LAN treatment ($P < 0.0005$ at all time points *vs.* basal value). After 24 months of therapy, controlled GH and IGF-I levels were achieved in 64%, 37%, and 78% and in 51%, 37%, and 70% of operated, irradiated, and *de novo* patients, respectively. A reduction in tumor size was documented in 5 of 23 *de novo* patients (22%). Among the 84 operated/irradiated with evident tumor remnant, significant shrinkage was documented in 5 patients (5.9%). Treatment was well tolerated by the majority of patients. Only 2 patients (1.7%) withdrew from LAN treatment due to severe side effects.

In conclusion, a 24-month treatment with slow release lanreotide (30 mg) is effective in reducing GH and IGF-I levels; furthermore, in *de novo* patients it induces disease control in 70% of patients and causes tumor shrinkage in 22% of them, with excellent compliance. These data suggest that LAN can be used in long-term treatment of acromegalic patients. (*J Clin Endocrinol Metab* **85:** 4099–4103, 2000)

ACROMEGALY IS A rare disease, characterized by excessive skeletal growth, soft tissue enlargement, and high morbidity and mortality, mainly due to cardiovascular, cerebrovascular, and respiratory abnormalities as well as to metabolic alterations (1–9). Moreover, increased incidence of benign and malignant tumors has been reported in acromegaly (2, 10–12), especially of colonic polyps and adenocarcinomas (10, 13–16). As the reduction of GH to "safe" levels was reported to reduce the mortality rate (11), GH/insulin-like growth factor I (IGF-I) hypersecretion needs to be well controlled. The current approach involves surgery, radiation, and pharmacological treatment with dopaminergic drugs or somatostatin analogs, alone or in combination (17, 18–26). The therapeutic goal is to improve clinical symptoms by suppressing GH and IGF-I hypersecretion, to achieve disease control (27–29), and to reduce tumor mass to correct or prevent local complication. Pharmacological treatment is generally applied after unsuccessful surgery in the presence of tumor remnant or invasiveness (30). Medical therapy using sc octreotide (OCT) two or three times a day has recently been eclipsed by the introduction of new long-acting formulation of somatostatin analogs, lanreotide (20–22, 31–37) and octreotide-LAR (25, 38–40), that overcome the inconvenience of multiple daily injections, which are unfavorable for patients during long-term treatment.

Lanreotide (Ipsen Laboratories), a slow release (SR-) formulation of the somatostatin analog BIM 23014, requiring an im injection every 7–14 days, has become available in the last few years in Italy. The effects of a short-term treatment with SR-lanreotide (LAN) on GH and IGF-I hypersecretion were similar to those obtained with octreotide (20–22, 31–35, 37), whereas the results of chronic treatment have been poorly investigated. In one study, LAN was reported to normalize GH and IGF-I hypersecretion in 27.7% and 63.6% of 22 patients treated for 24/36 months (22).

The aim of the present study was to evaluate the effects of

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a 24-month LAN treatment in a large group of acromegalic patients. The possibility that different therapeutic efficacy was shown by LAN in *de novo* patients compared with those previously treated with sc OCT was also investigated.

Subjects and Methods

Patients

One-hundred and eighteen patients with active acromegaly, 51 males and 67 females, aged 49.4 ± 15.4 yr (mean ± SD; range, 20–82 yr; median, 50 yr), were included in this open study that was performed at the Universities of Rome, Naples, and Turin (Italy). At study entry, acromegaly was clinically diagnosed on the basis of acral enlargement, patient interview, and comparison of photographs taken during a 1- to 2-decade span to date the onset of acral enlargement. Biochemical diagnosis was carried out by assessing high plasma GH levels (75.9 ± 8.1 mU/L), not suppressible below 3.0 mU/L after oral glucose tolerance test (OGTT), elevated age-matched plasma IGF-I values (693.6 ± 30.2 ng/mL). The OGTT was performed by measuring blood glucose and GH every 30 min for 2 h after the oral administration of 75 g glucose. In 4 patients with overt diabetes, OGTT was not performed. Ninety-one patients presented at diagnosis with microadenoma (mA), and 27 presented with macroadenoma (MA). In particular, 23 patients were newly diagnosed (*de novo* patients), and 95 patients had been treated with sc OCT before starting LAN treatment. Among these 95 unselected patients, 71 had also been previously operated on by the transsphenoidal or transcranial route (operated patients), whereas 24 of them had received conventional postoperative radiotherapy at least 1–5 yr before entering the study (irradiated patients). The evidence of pituitary adenoma or remnant tissue was confirmed in 84 of the 95 OCT-pretreated patients by magnetic resonance imaging (MRI) or computed tomography (CT) scan. Eleven patients had secondary empty sella after surgery and/or radiotherapy. The group of *de novo* patients included 15 women (age, 51.4 ± 4.9 yr; range, 22–77 yr; median, 50 yr) and 8 men (age, 45.1 ± 4.5 yr; range, 29–65; median, 46 yr); 8 patients had mA, and 15 had MA, with suprasellar and/or parasellar invasion in 12 patients. The most common visual field defect, represented by bitemporal hemianopsia, was present in 7 MA patients showing compression of the optic chiasm at radiological imaging; moreover, 3 of 23 *de novo* patients presented with growing headache. All patients gave their informed consent to the study, which was approved by all local ethical committees.

Treatment protocol

At study entry, plasma IGF-I levels were assayed in duplicate from a single sample, whereas the value of plasma GH was calculated as the mean of a 2- to 6-h blood sampling (0800–1000 h or 0800–1400 h, with 30-min sampling). Ninety-five patients were treated with OCT (Sandostatina, Novartis, Italy) at an initial dose of 0.15–0.30 mg/day, sc; this dose was increased to achieve normal GH and IGF-I levels up to 0.6 mg/day. Before starting LAN treatment, all patients underwent a 30- to 60-day wash-out period. A general physical examination was carried out before and every 3 months during treatment. All patients initially received LAN every 14 days over a 3-month period. Thereafter, in 54 patients showing persistently high hormone levels, LAN was administered every 10 days. During treatment, the final GH level was calculated as the average value from at least 3 blood samples collected, at 15-min intervals, just before the next im injection of LAN. The disease control after LAN treatment was considered when basal GH values were less than 7.5 mU/L together with IGF-I values within the normal range for age (27, 28). The time points of the study were defined as follows: T0, pretreatment evaluation in 118 patients; T1, after 6 months of treatment in 118 patients; T2, after 12 months of treatment in 114 patients; and T3, after 24 months of treatment in 99 patients. As radiotherapy induces hormone decrease over a prolonged time, GH and IGF-I levels were measured after 1-month LAN withdrawal in the 24 irradiated patients. All patients underwent gallbladder ultrasonography in the basal condition and after 6, 12, and 24 months of treatment.

Hormonal assays

Plasma GH levels were measured by immunoradiometric assay (HGH-CTK-IRMA Sorin, Saluggia, Italy). The sensitivity of the assay was 0.6 mU/L; 1 μg/L corresponds to 3 mU/L (28). The intra- and interassay coefficients of variation (CVs) were 4.5% and 7.9%, respectively. Plasma IGF-I was determined by RIA after acid-ethanol extraction; intra- and interassay CVs were 3.4–5.4% and 5.9–7.1%, respectively. In our laboratories, age-corrected normal ranges for IGF-I levels were less than 483 ng/mL (20–30 yr), less than 397 ng/mL (31–40 yr), less than 306 ng/mL (41–50 yr), and less than 249 ng/mL (>50 yr).

Radiological examination

A CT scan was carried out, before and after iv infusion of contrast medium using a third generation scanner with 3.5-s acquisition times, 1.5-mm-thick axial and coronal sections, and scout-views. MRI (0.5–1.0 Tesla) was carried out with T1-weighted SE sequences and 3-mm slides in coronal and sagittal sections before and after contrast enhancement with gadolinium-DTPA. CT scan or MRI was carried out in the basal condition and after 6, 12, and 24 months of LAN therapy. Significant tumor shrinkage was defined as a greater than 20% decrease in the pretreatment tumor volume calculated by the Di Chiro and Nelson formula: volume = height × length × width × $\pi/6$ (41).

Statistical analysis

Unless otherwise specified, all data are presented as the mean ± SEM. ANOVA, *t* test for unpaired data, Wilcoxon rank test, and χ^2 test were used when appropriate; $P < 0.05$ was considered significant. Statistical analysis was performed using StatView 5 software for Windows (SAS Institute, Inc., Chicago, IL).

Results

Nadir levels of GH and IGF-I during previous OCT treatment in the 95 patients were 19.2 ± 2.4 mU/L and 378.7 ± 18.3 ng/mL, respectively. In particular, controlled GH secretion was achieved in 32 patients (33.7%), whereas normal age-adjusted IGF-I levels were achieved in 45 patients (74.4%). All patients received LAN at the dose of 30 mg every 14 days for the first 3 months. In 54 of 118 patients (45.8%), the frequency of LAN injection was increased every 10 days, resulting in disease control in 17% of patients. In the 118 patients as a whole, circulating GH and IGF-I levels were significantly decreased during the 24 months of LAN treatment ($P < 0.0005$ at all time points *vs.* basal time; Figs. 1 and 2). In particular at T0, plasma GH levels were lower in irradiated patients ($P < 0.05$) than in those operated upon,

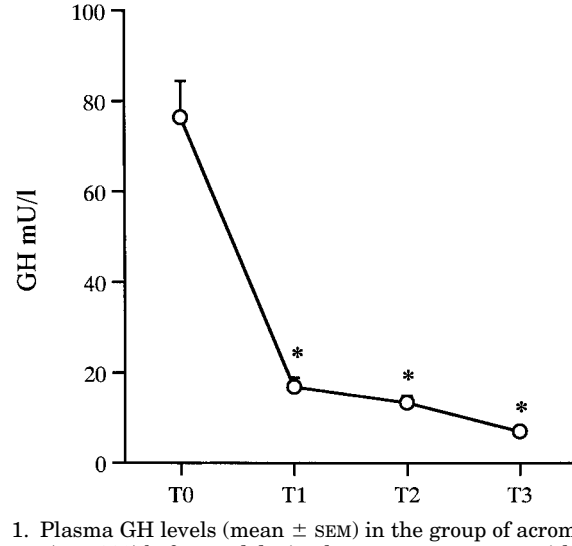

FIG. 1. Plasma GH levels (mean ± SEM) in the group of acromegalic patients (n = 118) before and during long-term treatment with LAN. *, $P < 0.0005$ *vs.* basal.

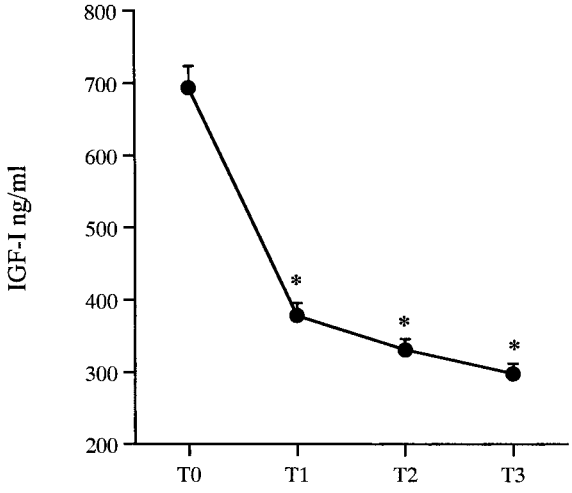

FIG. 2. Plasma IGF-I levels (mean ± SEM) in the group of acromegalic patients (n = 118) before and during long-term treatment with LAN. *, $P < 0.0005$ *vs.* basal.

whereas no difference in IGF-I levels was found in any group (Table 1). After 6 months of LAN treatment, GH levels were significantly lower in *de novo* patients ($P < 0.05$) than in those irradiated, whereas IGF-I levels were significantly lower in the operated and *de novo* patients than in the irradiated ones ($P < 0.005$; Table 1). After 12 months of LAN treatment, GH levels were significantly lower in *de novo* patients than in both operated and irradiated patients ($P < 0.05$ and $P < 0.0005$, respectively; Table 1). At this time point, operated patients had significantly lower GH levels than those irradiated ($P < 0.005$; Table 1). Similarly, IGF-I levels were significantly lower in operated and *de novo* patients than in those irradiated ($P < 0.05$, both; Table 1). After 24 months of LAN treatment, GH levels were significantly lower in *de novo* patients than in both operated and irradiated patients ($P < 0.05$ and $P < 0.005$, respectively; Table 1). At this time point, operated patients had significantly lower GH levels than those irradiated ($P < 0.005$; Table 1), whereas no differences were found in IGF-I levels.

On the basis of previous response to OCT therapy, patients submitted to LAN therapy were analyzed as responders and poor responders to OCT treatment. During long-term treatment with LAN, only 37 of 63 acromegalics poorly responding to OCT treatment did not achieve GH suppression (59%), whereas only 23 of 50 acromegalics poorly responding to OCT did not normalize IGF-I levels (46%) ($\chi^2 = 12.54$; $P < 0.0005$ and $\chi^2 = 11.95$; $P < 0.0005$, respectively).

Among the 23 *de novo* patients, significant tumor shrinkage was documented by CT and/or MRI in 5 patients (22%) after 3 (n = 2) and 6 (n = 3) months of LAN treatment. In particular, 5 of 7 patients improved their visual field, and 3 of 3 patients improved headache. Among the 84 operated/irradiated patients with documented tumor remnant at CT and/or MRI, tumor shrinkage was observed in 5 patients (5.9%), whereas no increase in tumor remnants was observed in poorly responsive patients during LAN treatment.

Moreover, when patients were grouped into mA and MA, significantly lower GH plasma levels were found in mA patients basally and after 6 and 12 months of treatment ($P <$

TABLE 1. GH and IGF-I levels before and during LAN therapy (mean ± SEM) in separately groups of operated, irradiated, and *de novo* patients

Patients	Age (yr)	Plasma GH levels (mU/L)				Plasma IGF-I levels (ng/mL)			
		T0	T1	T2	T3	T0	T1	T2	T3
Operated	49.5 ± 15.2	90.3 ± 12.3 (71)	17.1 ± 3.0 (71)	12.3 ± 1.8 (70)[a]	6.3 ± 0.6 (58)[a]	705.8 ± 43.5 (71)	359.8 ± 19.8 (71)[a]	321.7 ± 17.5 (70)[b]	290.3 ± 17.8 (58)
Irradiated	50.7 ± 13.4	46.2 ± 5.1 (24)[c]	22.8 ± 4.8 (24)	24.3 ± 4.5 (22)	11.4 ± 1.5 (19)	710.4 ± 62.8 (24)	501.6 ± 48.3 (24)	407.5 ± 35.8 (22)	343.6 ± 35.7 (19)
De novo	49.2 ± 17.0	65.1 ± 11.4 (23)	9.0 ± 1.5 (23)[b]	5.1 ± 0.9 (22)[c,d]	3.6 ± 0.6 (22)[a,c]	638.5 ± 41.5 (23)	305.1 ± 26.3 (23)[a]	284.3 ± 26.7 (22)[b]	255.6 ± 44.6 (22)

In *parentheses* are reported the total number of patients at each time point.
[a] $P < 0.005$ *vs.* irradiated.
[b] $P < 0.05$ *vs.* irradiated.
[c] $P < 0.05$ *vs.* operated.
[d] $P < 0.0005$ *vs.* irradiated.

0.05), whereas significantly lower IGF-I plasma levels were found in mA patients after 6, 12, and 24 months of treatment ($P < 0.05$; data not shown).

During OCT treatment, abdominal discomfort after the first injections was reported by 64 patients, and steatorrhea was reported by 17 patients. These side effects disappeared spontaneously in 26 patients and after treatment with pancreatic enzymes in some subjects. After the first injection of LAN, abdominal discomfort was reported by 45 and steatorrhea by 10 patients. Fifty of 118 patients reported moderated discomfort at the injection site, lasting less than 24–48 h. During LAN treatment period only 2 patients reported serious side effects (worsening of headache, severe abdominal pain, and steatorrhea) that forced them to withdraw from treatment after 6 months. In all of the remaining 116 patients, side effects were mild and spontaneously disappeared 1–4 days after the first injection, and specific treatment with pancreatic enzymes was required only in 5 patients. Gallbladder ultrasonography was performed in all patients before and during the 24-month LAN treatment; gallstones were detected in 4 patients, and sludge was found in 10 patients. Gallstones and sludge disappeared spontaneously in 1 and 5 patients, respectively, and after ursodehoxicholic acid treatment in the remaining 3 and 5 patients. No patient developed signs of symptomatic colelithiasis or colecistitis.

Discussion

Acromegaly is a slow-developing disease featured by chronic and progressive disability and, when left untreated, increased mortality (1–16). Long-term treatment with sc OCT has proven very effective in controlling GH/IGF-I hypersecretion and has produced safe hormone levels in one third to one half of patients in different series (28). However, the need for multiple daily administrations produced compliance problems in the majority of patients. The development of new long-acting somatostatin analogs has overcome this inconvenience (20–22, 25, 31–40). As LAN has become available only in recent years, few data have been reported on its effectiveness in long-term treatment (22). In this study we evaluated the effectiveness and tolerability of chronic treatment with LAN in a large series of acromegalic patients. Our results demonstrated that LAN induced a significant suppression of circulating GH and IGF-I levels in the great majority of patients, allowing them to achieve disease control in 77% (GH) and 63% (IGF-I) of all 118 patients after 24 months of therapy.

It is relevant to note that this study, in contrast with others, included patients unselected with respect to a previous positive response to OCT treatment (33, 42).

Among the 95 patients previously treated with OCT, 63 (66%) did not achieve disease control during OCT treatment. In contrast with the findings of another study (37), long-term treatment with LAN seems to improve responsiveness in patients poorly responsive to OCT. GH and IGF-I levels during the 24-month LAN treatment period were significantly lower ($P < 0.005$) in OCT-responsive than in OCT poorly responsive patients, confirming the persistent presence of a group of somatostatin analog-resistant patients. It is important to underline that all patients who responded to OCT also responded to LAN treatment; furthermore, an additional group of patients poorly responsive to OCT became responsive to LAN. In the first study (37) addressing a similar issue, the response to LAN treatment was evaluated during a period of only 6 months. It is, therefore, likely that a longer treatment period with the slow release formulations of somatostatin analogs can produce long-lasting suppression of GH and IGF-I levels. On the basis of previous studies (21, 33), all patients were admitted to LAN treatment at a dose of 30 mg every 14 days for the first 3 months. After this period, in 54 of 118 patients the frequency of LAN injection was increased every 10 days, resulting in disease control in 17% of patients. This indicates that the first modification of the frequency of injection is better performed after 3 months of treatment to achieve a cumulative effect of repeated injections (33, 43). In our group of 118 acromegalic patients, normal GH levels after 6, 12, and 24 months of treatment were achieved in 31%, 56%, and 77% of patients, whereas normal IGF-I levels were achieved in 30%, 47%, and 63% of patients, respectively. Such a discrepancy could be explained either by the presence of physiological fluctuations in GH levels or by other IGF-I control factors that were not GH related (22, 31, 35).

The prevalence of patients not achieving disease control was significantly lower ($P < 0.005$) in *de novo* patients (22%) than in those operated upon (36%) and irradiated (63%).

Shrinkage of GH-secreting adenomas has been reported in about 30–50% of acromegalic patients treated with OCT (42, 44). In our series, tumor shrinkage could be documented in 5 of 23 *de novo* patients (22%). A similar percent shrinkage rate was reported in a previous study of 22 patients with acromegaly treated for 1–3 yr with LAN (22). Moreover, in 5 of 7 patients, visual field improved as a direct consequence of tumor shrinkage; this points out that about one quarter of *de novo* patients with pretreatment bitemporal hemianopsia did not achieve adequate tumor shrinkage to relieve visual compromise.

The better response observed in *de novo* patients compared with operated and irradiated patients could be explained by the possible presence of some modification caused by surgery and radiotherapy, such as changes in vascular bed, postsurgery fibrosis, alteration in the density of somatostatin receptors, or wider GH fluctuations during previous OCT therapy. On the other hand, we do not know whether the *de novo* group contained a higher percentage of patients responsive to OCT therapy, potentially leading to a higher success rate for this group.

The present study suggests that previous treatment with radiotherapy induced partial resistance to somatostatin analogs therapy, as shown by the presence of higher GH and IGF-I levels throughout the 24-month period in the group of irradiated patients; this aspect supports the better response of *de novo* patients to LAN therapy. This is important information, suggesting that radiotherapy may act as a negative prognostic factor regarding the LAN response. This picture strengthens the concept that previously operated or *de novo* patients are characterized by a better outcome, in terms of normal GH and IGF-I plasma levels, than patients previously treated with radiotherapy.

Controlled GH levels were achieved in 78% and 58% of mA and MA patients, respectively ($P < 0.05$).

LAN was well tolerated during the entire study period in all except two patients (1.7%) who withdrew from treatment after 6 months due to the occurrence of severe side effects. The more frequent side effects reported by patients were represented by minor digestive problems such as nausea, abdominal discomfort, and steatorrhea within the first 2–3 days after the injection. The presence of these side effects did not induce any change in the frequency of LAN administration. Moreover, the presence of abdominal discomfort and steatorrhea was not related to the different regimen of LAN administration. The prevalence and frequency of side effects are superimposable to those reported in previous studies (21, 31, 33, 42).

In conclusion, this 24-month follow-up study demonstrated that the somatostatin analog SR-lanreotide (30 mg) was effective in controlling GH and IGF-I hypersecretion in most acromegalic patients, especially in *de novo* patients. Previous radiotherapy treatment seems to induce partial resistance to LAN therapy. The higher prevalence of disease control in *de novo* patients suggests that LAN can be an option as first line therapy in such patients as well as a second line treatment after unsuccessful surgery, as proposed for sc OCT (44), and is accompanied by excellent patient compliance in long-term treatments.

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