Lanreotide 60 mg, a New Long-Acting Formulation: Effectiveness in the Chronic Treatment of Acromegaly

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Lanreotide (LAN) 60 mg (LAN60), a new long-acting formulation of LAN alleged to suppress GH/IGF-I hypersecretion for 28 d in acromegalic patients, was administered in a prospective open multicenter study to 92 patients with active acromegaly (61 women and 31 men, aged 20–79 yr). LAN60 was given as adjuvant treatment (AT) in 62 patients; the other 30 patients [primary treatment (PT)] were *de novo* (n = 20) or previously treated only by pharmacotherapy (n = 10). After wash-out from previous treatments, LAN60 was started im every 28 d for 3 injections; the dose was then individually tailored, aiming at lowering GH to less than 2.5 μg/liter and IGF-I to the normal range. After a median follow-up of 24 months (range, 6–48 months), IGF-I normalized in 65% of patients, decreasing from 199 ± 8% (expressed as a percentage of the upper limit of normal range; mean ± SE) to 87 ± 4% ($P < 0.0001$). GH fell to less than 2.5 μg/liter in 63% of patients and to less than 1 μg/liter in 25%, decreasing from 20 ± 3 to 3 ± 0.4 μg/liter ($P < 0.0001$). A progressive increase in the rate of IGF-I normalization was observed (from 49% at 1 yr to 77% at 3 yr). The rate of GH/IGF-I normalization was 72% at 36 months by Kaplan-Meier analysis. No tachyphylaxis was observed throughout the study. Shortening the interval between injections to 21 d improved GH/IGF-I suppression. PT and AT patients achieved similar final GH/IGF-I levels and rates of normalization. Tumor shrank in 39% of assessable patients and in 50% of PT. Plasma glucose levels did not change, and high density lipoprotein cholesterol increased (by 19.3 ± 5.1%; $P = 0.0215$). Gallstones appeared or worsened in 13% of patients. LAN60 is a new, very effective and long-lasting formulation for the treatment of acromegaly. The persistence of a powerful suppression of GH/IGF-I levels, the progressive increase in the rate of IGF-I normalization, and the similarity in the efficacy achieved in PT and AT patients point to a role for LAN60 in the primary treatment of acromegaly. (*J Clin Endocrinol Metab* 88: 5258–5265, 2003)

ACROMEGALY IS AN insidious chronic disease caused by unrestrained hypersecretion of GH and IGF-I (1). It is associated with increased morbidity and reduced life expectancy, mostly due to cardiovascular disease (2). Epidemiological studies have shown that the increased mortality associated with active acromegaly is reversed to normal rates, after achieving safe GH levels (*i.e.* <2.5 μg/liter) regardless of the therapeutic approach used (3, 4).

Neurosurgery (NS) is still usually considered the first choice treatment (5). Pharmacotherapy has been employed to reduce GH/IGF-I hypersecretion in patients unsuitable or unwilling to undergo NS, after its failure, or in selected cases as primary treatment (PT) (6). Depot somatostatin analogs (SA), such as lanreotide-SR (LAN) 30 mg (7) and octreotide (OC) long-acting repeatable (OC-LAR) (8), have been consistently shown to be able to reduce hormonal hypersecretion in most patients and to normalize IGF-I levels in many of them. Recently, Freda (9), summarizing the literature data on the topic, showed the achievement of safe GH levels in 56%

of patients treated with OC-LAR and in 49% of those treated with LAN 30 mg (LAN30). The respective figures for IGF-I normalization were 66% and 48%. Moreover, SA have been demonstrated to induce tumor shrinkage (up to 50% of basal volume) in 30% of the patients.

LAN 60 mg (LAN60; Ipsen-Beaufour, Milan, Italy) is provided as a slow-release formulation of LAN, encapsulated in microspheres of polylactide-polyglycolide copolymers, to be dissolved in 2 ml isotonic saline just before administration. The new formulation of 60 mg is prepared using a slightly more hydrophobic polymer matrix. The main difference between 30- and 60-mg formulations consists in the amount of microparticles filled into the vials, all components being essentially the same.

The aim of this study was to evaluate the effects of prolonged treatment with LAN60 on GH/IGF-I levels and tumor size in a large series of acromegalic patients.

Subjects and Methods

Patients

Ninety-two acromegalic patients (61 women and 31 men; aged 20–79 yr; median, 50 yr), attending 5 different centers in Italy, entered this prospective open study. Inclusion criteria were active disease (according to the clinical picture, GH levels not suppressible to <1 μg/liter after an oral glucose load and elevated age-adjusted IGF-I levels) and sensitivity

to SA (arbitrarily defined as GH and/or IGF-I decrease of at least 20%, compared with the baseline, after a 3- to 6-month treatment challenge).

LAN60 was administered as adjuvant treatment (AT) to 62 patients; 31 had been previously submitted to NS, 4 to radiotherapy (RT), and 27 to both. NS had been performed at least 6 months before the start of LAN60 treatment, and RT at least 5 yr before. In 30 patients SA had been administered as primary treatment (PT): among them, 20 were *de novo*, and 10 were previously treated only by other SA (OC or LAN30). At neuroradiological pituitary imaging, 21 had macroadenoma, 12 had microadenoma (in 8 invading the cavernous sinus), 41 had remnant of pituitary adenoma, 13 had empty sella, and 5 had normal pituitary imaging. Sixteen patients had mildly elevated serum PRL levels, not requiring dopamine agonist treatment.

Any drug treatment aimed at decreasing GH hypersecretion had been withdrawn at least 3 months before the start of the study, whereas replacement treatment with L-T$_4$, cortisone acetate, testosterone, or ethinyl estradiol with progesterone was regularly carried out as needed.

Each patient gave informed consent after full explanation of the purpose of the study, which was approved by each local ethics committee, and procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 1983.

Protocol

Treatment with LAN60 was started at the dosage of 60 mg, administered im every 28 d for three injections. Thereafter, the LAN60 schedule was individually tailored, aiming at achieving normal age-adjusted IGF-I levels and a mean GH less than 2.5 μg/liter. The interval between injections was shortened to 21 d and then to 14 d when IGF-I remained above the age-matched normal range. When IGF-I decreased below 50% of the upper limit of normal range (ULNR), the interval between the following injections was progressively lengthened by up to 35–75 d.

Control evaluations and titration of dose were performed at 3-month intervals on an out-patient basis on the day of administration of the drug, before the injection was given, with a careful clinical evaluation (detailing frequency and intensity of headache, paresthesias, perspiration, swelling, fatigue, arthralgia, and snoring, and recording adverse events) and blood analysis. Blood samples were collected in the morning hourly for at least 3 h after an overnight fast and rest while the patients were supine and awake, with an indwelling needle inserted into an antecubital vein and kept patent by slow infusion of saline. GH concentrations were assayed for each sample (in *Results*, the reported value is the mean of all samples), and IGF-I levels were assayed for the first sample.

Neuroradiological control aimed at evaluating tumor size changes was performed in the PT group in patients with macroadenoma or microadenoma and in the AT group in patients with large remnant (>15 mm) before the start of treatment, at 6-month intervals during the first year, and yearly thereafter.

Liver ultrasound examination was performed before the start of treatment and yearly thereafter.

Methods

Hormones were measured in-house at each participating center using commercially available reagents. GH levels were assayed with immunoradiometric methods similar among the different centers: detection limit at least 0.2 μg/liter, intra- and interassay coefficients of variation below 4.5 and 8%, respectively. Due to the multicenter nature of the study, IGF-I concentrations are expressed as a percentage of the ULNR (mean + 2 SD), as each laboratory defined it.

Plasma glucose, glycated hemoglobin, total cholesterol, and high density lipoprotein (HDL) cholesterol were assayed with standard methods in each center with variable reference range, so that they are expressed only as percent change compared with the baseline.

Magnetic resonance imaging scans were performed at each participating center using an equipment of at least 1.5 Tesla, using T1-weighted thin sections (3 mm thick, with 0.1 factor distance interleaved), obtaining sagittal and coronal images of the pituitary before and after iv gadolinium. The patients were placed in the same position in each imaging occasion to obtain slices as comparable as possible. All parameters were kept constant for each imaging session. The neuroradiologists evaluating the scans were blind to the clinical and endocrine data. On each scan the largest diameter of the tumor was measured on coronal [vertical diameter (V)], and axial sections [anteroposterior (AP) and transverse (T)], calculating the approximate volume of the adenoma, after correction for magnification factor, as the volume of a rotating ellipsoid, with the formula (10): volume = π (V × AP × T)/6. The shrinkage of the tumor was arbitrarily considered significant when its volume was reduced by at least 25% compared with pretreatment values.

Statistical analysis

Values are expressed as the mean ± SE unless otherwise stated. Analyses were performed by GB-Stat 6.5.4 PPC on raw data or after transformation of hormonal data as a percentage of the baseline.

Data were analyzed by parametric tests, because they passed preliminary Kolgomorov-Smirnov test for normality. Continuous variables were analyzed by completely randomized ANOVA, followed by Newman-Keuls test, ANOVA for repeated measures, followed by Dunn's test, *t* test for paired or unpaired data, or Pearson correlation test as appropriate. Multiple regression analysis and logistic regression analysis were performed only on data that were significantly correlated in pairwise analysis. Categorical variables were analyzed by χ^2 test with Fisher's correction when appropriate. Survival analysis was performed by Kaplan-Meier analysis, and differences between subgroups were evaluated by log-rank test. All statistical tests were two-tailed, and $P < 0.05$ was considered significant.

Results

Patients were followed-up for a median period of 24 months (range, 6–48 months). No patient was lost to follow-up, which ended in July 2002. The clinical picture (headaches, paresthesias, perspiration, swelling, fatigue, arthralgia, and snoring) improved in all patients (data not shown).

GH/IGF-I changes

Figure 1 shows that LAN60 significantly suppressed GH and IGF-I levels at the first evaluation. Mean GH decreased from 20.2 ± 2.9 μg/liter at the baseline to 5.7 ± 0.7 μg/liter at 3 months and remained suppressed until the end of the follow-up (final value, 3 ± 0.4 μg/liter; $P < 0.0001$). IGF-I fell from 199 ± 8% to 105 ± 6% ULNR at 3 months and to 87 ± 4% ULNR at the end of the observation period ($P < 0.0001$). Even though after 6 months of treatment the drug dose was not significantly increased in the whole group, IGF-I levels were progressively further suppressed after the first 3–6 months of treatment, whereas GH levels remained constant. No tachyphylaxis was observed throughout the study.

The *inset* in Fig. 1 shows that LAN60 treatment decreased GH to less than 2.5 μg/liter in 58 patients (63%) and to less than 1 μg/liter in 23 patients (25%). Normal age-matched IGF-I levels were reached in 60 patients (65%).

Figure 2 shows a progressive increase in the rate of IGF-I normalization (49% at 12 months, 69% at 24 months, 77% at 36 months) and in the rate of GH to less than 2.5 μg/liter (46%, 68%, and 81%, respectively) throughout the follow-up. By Kaplan-Meier analysis, the rate of both safe GH (<2.5 μg/liter) and IGF-I normalization was 72% at 36 months. Neither basal hormonal levels nor length of follow-up were different between patients who achieved hormonal normalization and those who did not. Discordant results were observed in 22 patients; in 12 of them GH remained above 2.5 μg/liter despite IGF-I normalization, whereas in 10 patients IGF-I levels were still above the age-matched normal range despite safe GH levels.
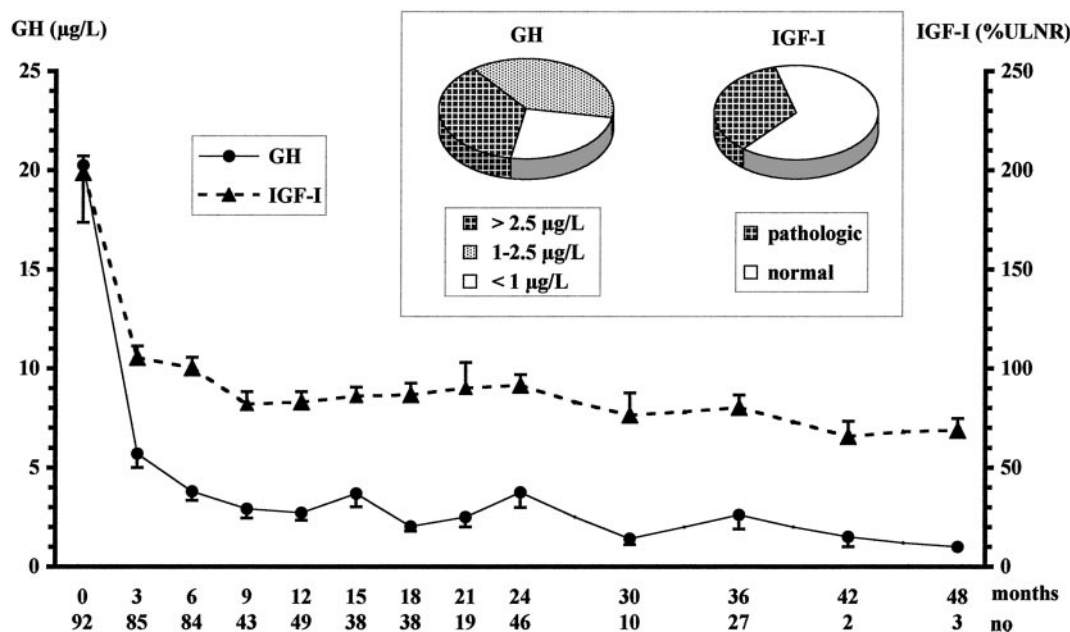
FIG. 1. GH (*left vertical axis*, ●) and IGF-I (*right vertical axis*, ▲) levels (mean ± SE) during treatment. In the *inset* the percentages of hormonal normalization at the last evaluation are shown: on the *left*, GH less than 1 µg/liter (*empty*), between 1–2.5 µg/liter (*dotted*), and above 2.5 µg/liter (*hatched*); on the *right*, normal and pathological IGF-I (*empty* and *hatched*, respectively).
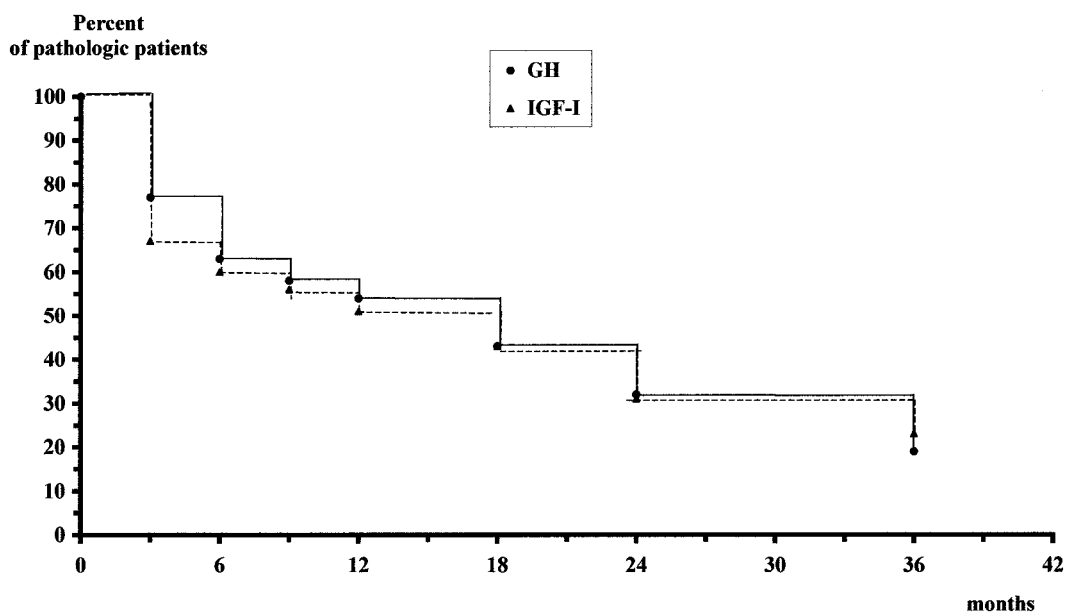

FIG. 2. Kaplan-Meier analysis. Achievement of safe GH levels is depicted by a *continuous line*, and IGF-I normalization by a *broken line*.

Figure 3 shows that patients starting from higher basal GH levels (split according to basal quartiles) achieved greater percent GH suppression. In contrast, no difference in percent suppression was shown for IGF-I. However, the evaluation of final outcome showed a similar rate of safe GH in the four subgroups and a higher rate of IGF-I normalization in patients with the lowest basal GH ($P = 0.0399$).

LAN60 dose and schedule

The final LAN60 schedule was every 28 d in 42 patients (45.6%) and every 21 d in 24 patients (26%); it was shorter than 21 d in 8 patients (8.7%, namely every 14 d in 6 and every 10 d in 2) and longer than 28 d (up to 75 d) in 18 patients (19.6%).

Shortening the interval between LAN60 injections from 28 to 21 d in 16 patients induced a higher suppression of both IGF-I (from 130 ± 12% to 108 ± 10% ULNR; $P = 0.0186$) and GH levels (from 9.6 ± 1.4 to 5.4 ± 0.9 µg/liter; $P = 0.0229$) after a comparable follow-up.

In patients attaining IGF-I levels less than 50% ULNR during treatment, the interval between each subsequent injection was lengthened. The same suppression was main-

FIG. 3. *Left panel*, Percent decrease in GH/IGF-I (mean ± SE) according to basal GH quartiles: □, first quartile; ▦, second quartile; ▨, third quartile; ■, fourth quartile. *Right panel*, Percentage of patients achieving safe GH and normal age-matched IGF-I according to basal GH quartiles. *, $P < 0.05$ *vs.* lower quartiles.
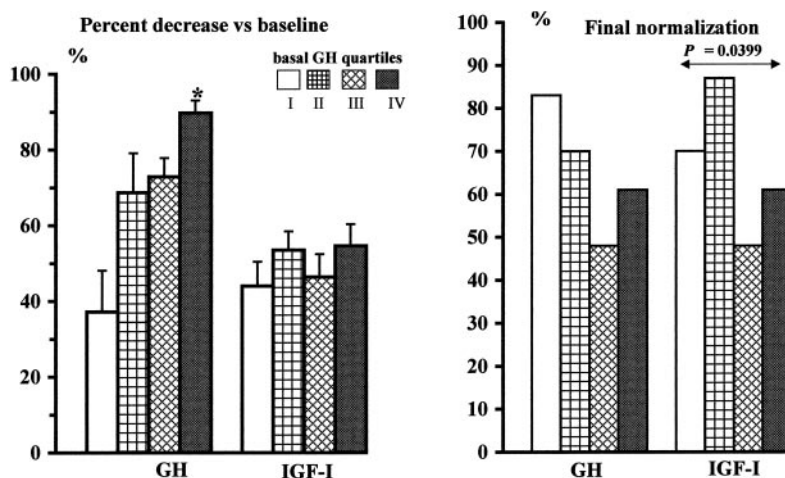
tained in 16 of 18 patients after interval prolongation of up to 75 d (data not shown).

A progressive suppression of IGF-I levels ($P < 0.01$ from the third month), but not of GH, was observed in 46 patients who maintained a fixed schedule of LAN60 (*i.e.* no change in dosage or time interval between injections). This finding was observed even in the subgroup of 29 patients not previously treated with RT (63% of this group; data not shown).

Influence of previous treatments and age

Basal IGF-I levels were higher in PT patients than in AT ($232 \pm 16\%$ *vs.* $182 \pm 9\%$ ULNR; $P = 0.0093$), whereas mean basal GH levels were not different (18.2 ± 3.1 *vs.* 21.2 ± 4 μg/liter; $P = 0.557$). LAN60 treatment achieved similar mean final values [GH, 2.7 ± 0.6 *vs.* 3.1 ± 0.5 μg/liter ($P = 0.5752$); IGF-I, $93 \pm 8\%$ *vs.* $85 \pm 5\%$ ULNR ($P = 0.3885$)] as well as similar rate of normalization [GH < 2.5 μg/liter: 19 of 30, 63%, *vs.* 41 of 62, 66% ($P = 0.7918$); normal IGF-I: 21 of 30, 70%, *vs.* 40 of 62, 65% ($P = 0.6019$)] in the 2 subgroups. Figure 4 shows individual GH and IGF-I values. The results were similar in patients previously irradiated or not ($P = 0.6088$ and $P = 0.437$ for GH and IGF-I, respectively, by log-rank analysis). Figure 5 shows results obtained in patients treated with LAN60 at fixed dosages throughout the follow-up, according to previous irradiation status.

As for age, elderly patients (*i.e.* older than 50 yr, median value of the series) had lower basal GH levels than younger ones (9.8 ± 1.3 *vs.* 30.7 ± 5.2 μg/liter; $P = 0.0003$) despite a higher rate of PT (85% *vs.* 50%). GH suppression was similar in the two subgroups, so that final values were still lower in elderly (2 ± 0.2 *vs.* 4 ± 0.8 μg/liter; $P = 0.0165$). By contrast, IGF-I levels were higher in elderly at the start of treatment ($216 \pm 12\%$ *vs.* $182 \pm 11\%$ ULNR; $P = 0.046$), but the final levels were similar ($84 \pm 5\%$ *vs.* $91 \pm 7\%$ ULNR; $P = 0.4042$). The drug dose was 63 ± 4 mg every 28 d in the elderly and 78 ± 6 mg every 28 d in the younger ones ($P = 0.0399$). The same results were found by comparing patients older than 65 yr with the younger ones.

Tumor size

Tumor size reduction (range, 25–50% of basal volume) was observed at magnetic resonance imaging in 28 of the 72 assessed patients (39%). Shrinkage of macroadenomas was slightly more evident than in microadenomas or remnant tumors (52% *vs.* 18% and 37.5%, respectively; $P = 0.0753$). By logistic regression analysis no variable was correlated to tumor size reduction (basal or final hormonal levels, length of follow-up, size of adenoma, drug dose, or previous treatment). Tumor shrinkage was observed in 11 of 22 patients in the PT group (50%).

Adverse effects

No patient withdrew from the study because of adverse effects of LAN60. There were no significant changes in routine biochemistry and hematology. Fasting glucose levels did not change significantly. Among the 17 diabetic patients hyperglycemia improved in 6 and worsened in 5. An increase above the upper normal level of glycated hemoglobin occurred in 6 nondiabetic patients (8%). Similarly, total cholesterol levels did not change (by $-1.5 \pm 2.5\%$). In contrast, HDL cholesterol increased by $19.3 \pm 5.1\%$ ($P = 0.0215$). Liver ultrasound examination detected gallstones before LAN60 treatment in 12 patients; 10 patients (11%) showed new biliary abnormalities (sludge or stones) during LAN60 treatment. Eight patients (8.7%) complained of transient gastrointestinal side-effects (nausea, abdominal bloating, and steatorrhea) that did not require withdrawal from treatment. Local pain at the injection site was reported by a few patients, decreasing after the following injections in most.

Discussion

Even though NS is still regarded as first-line treatment for acromegaly in most patients (6), the availability of SA (7, 8, 11) affords the clinician the ability to individualize treatment in single patients, aiming at curing, as defined by recent criteria (12), *i.e.* GH below 2.5 μg/liter and normal age-matched IGF-I levels.

LAN, the first developed long-acting SA (7), has shown its effectiveness in several reports. Clinical experience in large series of acromegalic patients (13–25) showed the efficacy of the 30-mg formulation, injected every 14 d, in reducing GH/IGF-I hypersecretion in most patients and in inducing hormone normalization in the majority of cases. Hormonal changes are accompanied by consistent clinical amelioration;
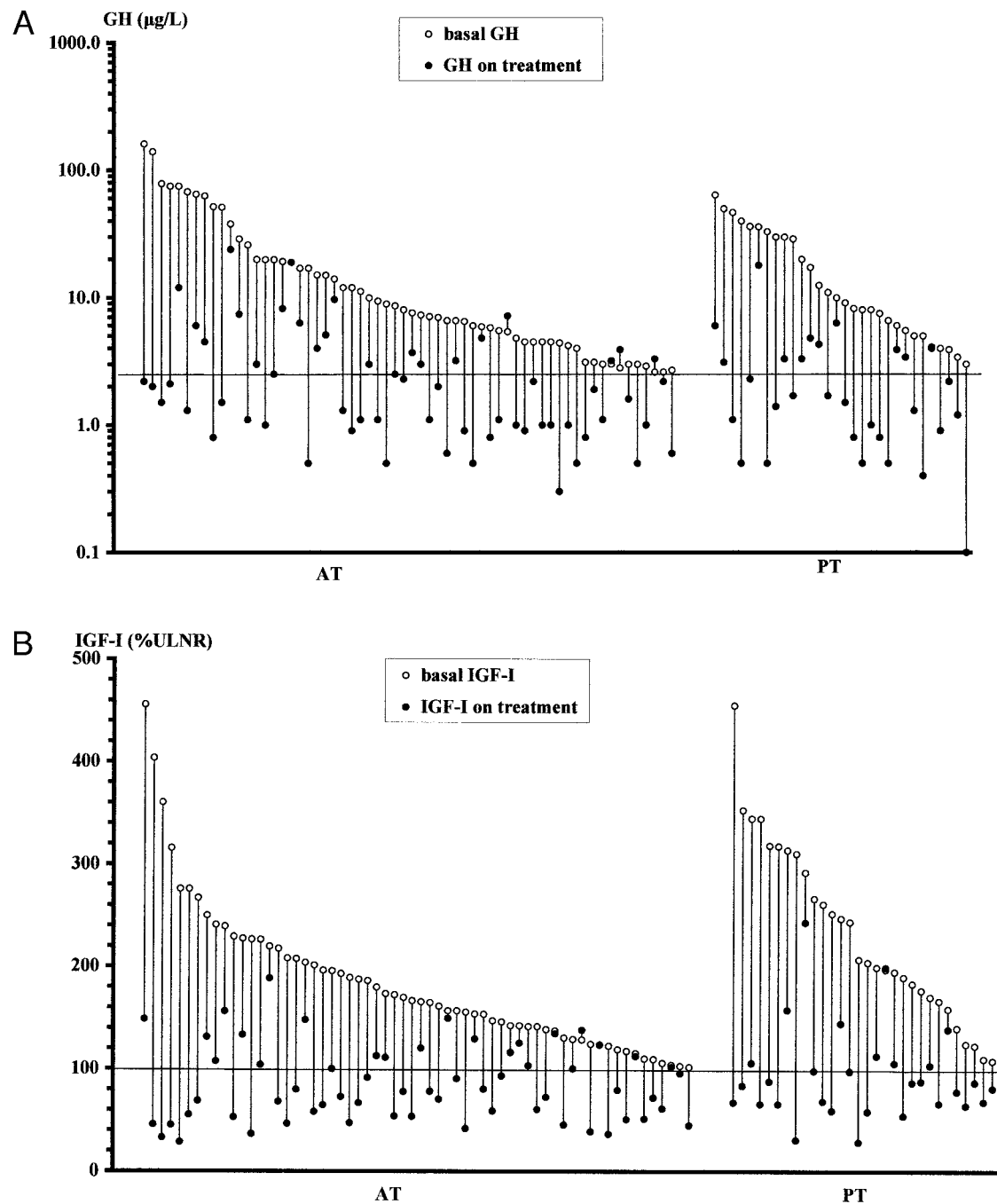
FIG. 4. Individual GH (A; log scale) and IGF-I (B) levels before (○) and at the final evaluation on LAN60 (●). The *horizontal line* is set at 2.5 μg/liter in A and at 100% ULNR in B.

both clinical score of symptoms (15) and quality of life (26) have been reported to improve substantially during LAN30 treatment as well as peripheral organ disease at the cardiovascular level (27–29), joints (30), and prostate (31).

The development of the 60-mg formulation of LAN, with a more prolonged duration of action (extending to 28 d according to the manufacturer), further improves patients' convenience and compliance. In this prospective, open, multicenter study we show the effectiveness of LAN60 in obtaining safe GH in 63% of patients and IGF-I normalization in 65% at the final evaluation, without tachyphylaxis in any.

Reports on LAN60 chronic treatment in acromegalic patients are still limited. Cozzi *et al.* (32) obtained safe GH levels after a 6-month treatment in 48% of their series (2 of 8 *de novo* patients and 8 of 13 patients directly switched to LAN60 after a previous LAN30 treatment). Ambrosio *et al.* (33) attained GH below 2.5 μg/liter after 8 months in 65% of 20 patients, all previously treated with LAN30. As for IGF-I, Cozzi *et al.* (32) reported its normalization in 76% of their series with a fixed 28-d schedule, whereas Ambrosio *et al.* (33) achieved normalization in only 35% of their patients despite shortening the interval between injections to 21 d in half of them. In
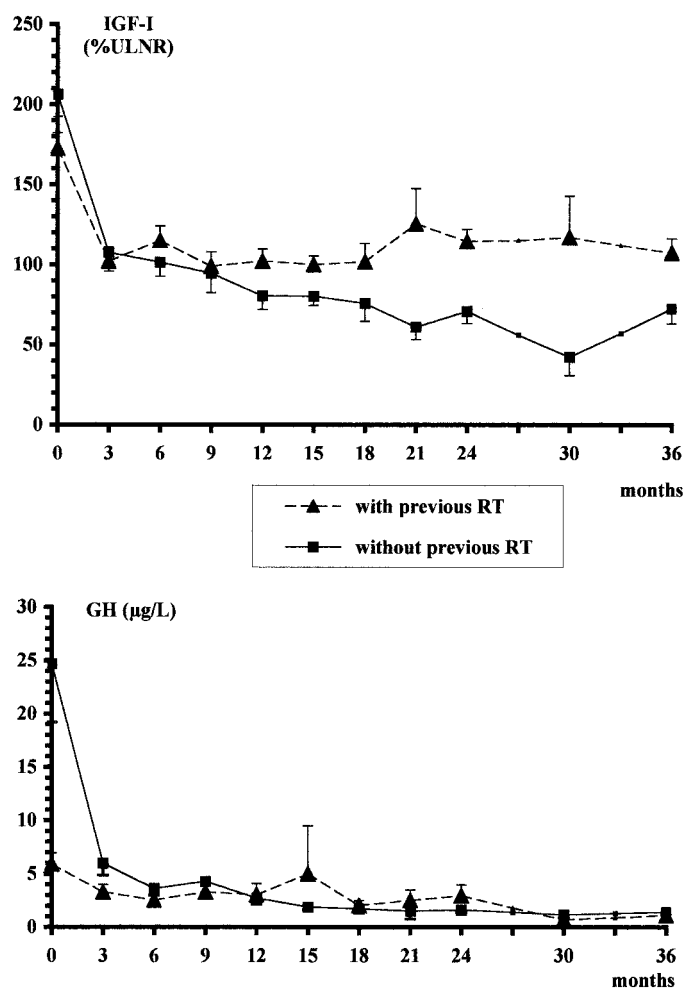
FIG. 5. GH (*lower panel*) and IGF-I (*upper panel*) levels (mean ± SE) during LAN60 treatment in patients previously irradiated (*triangles* and *broken lines*, n = 17) or not (*squares* and *continuous lines*, n = 29). The drug dose was not changed after the initial titration.

the current study we found that the prolonged LAN60 administration progressively suppressed IGF-I levels regardless of any change in drug schedule, even after excluding from analysis previously irradiated patients. Furthermore, we found a higher prevalence of IGF-I normalization (namely 49% after 1 yr, 69% after 2 yr, and 77% after 3 yr) compared with previous studies.

In poorly sensitive patients no substantial improvement in GH/IGF-I suppression was observed after either increasing drug dose and/or shortening the interval between injections. Conversely, in very sensitive patients (18% of the series) the same GH/IGF-I suppression was maintained by prolonging the interval between injections up to 75 d regardless of previous RT. This finding should be taken into account when evaluating the single patient, who needs an accurate individual titration of drug dose for optimization of treatment and cost-saving (34).

In our study the results of treatment were only partially related to basal GH levels. Indeed, patients starting from lower basal GH levels achieved lower final GH levels, but the figure of safe GH was similar to that obtained by the patients with the highest basal values. In addition, patients starting

from higher basal GH levels obtained the greatest percent GH decrease *vs.* basal levels, pointing to an excellent sensitivity to treatment regardless of basal hormonal levels. The rate of normalization of IGF-I was related to basal GH levels.

The final outcome was similar between patients of the PT and AT groups for both GH/IGF-I suppression and rate of normalization. PT of acromegaly was first shown to be as effective as AT in a large multicentric retrospective not randomized study reported by Newman *et al.* (35), comparing OC results in patients previously submitted to noncurative surgery with those who were not. A prospective randomized trial comparing PT and AT has not yet been performed, but many data support the choice for PT in acromegaly (36). Neurosurgical results are strictly operator dependent (37), and nearly half of patients with macroadenoma, particularly the invasive type, are not cured even in the most-experienced hands (38). Moreover, the results of RT have been largely debated in recent years, with some researchers reporting a low prevalence of IGF-I normalization even after a very prolonged follow up (39, 40). Also, radiosurgical techniques such as the γ-knife, which is still under investigation, do not seem to fulfill early promises (41). By contrast, promising results of PT have been recently reported (42–45).

Our results point to a greater sensitivity of elderly patients to LAN60 despite a greater severity of disease, as shown by higher basal IGF-I levels in elderly than in younger patients, the posttreatment superimposable final GH/IGF-I levels, and the rate of normalization, notwithstanding the lower drug dose employed in elderly patients. This finding was previously reported for both short-acting (46) and long-acting (47) OC treatments.

Tumor size reduction was observed in 39% of the patients in this series. The prevalence of shrinkage increased to 50% when considering only PT patients. Tumor shrinkage was reported to occur in different proportions in literature series, ranging from 17% in the patients treated with LAN30 to 43% in the patients treated with OC-LAR (9). When only PT patients treated with depot SA are considered, the rate of shrinkage is much higher: 80–88% in the series treated with OC-LAR (42, 45) and 78% in those treated with LAN60 (32). These data were recently confirmed by prospective studies; in the United Kingdom Primary Octreotide Study (44) tumor shrank in all 27 patients.

As for side-effects, LAN60 treatment did not significantly influence glucose metabolism in this series.

It is worth noting that HDL cholesterol, a well known protective factor for cardiovascular disease (48), increased during treatment in our patients. This finding was previously reported during OC treatment (49), and LAN30 treatment (29), adding to the already recorded treatment-induced changes in cardiac function (28, 29, 50), pointing to an amelioration of the global cardiovascular risk profile.

Treatment was well tolerated in all patients. New biliary abnormalities developed in 11% of the patients of the series, in agreement with previous reports (9).

In conclusion, our prospective study in a large series of acromegalic patients showed the efficacy and tolerability of chronic LAN60 treatment, without tachyphylaxis in any, even after a very prolonged follow-up. Safe GH was achieved in 63% of the PT and in 66% of the AT patients; normal IGF-I

was achieved in 70% and 67%, respectively. Tumor size shrinkage was obtained in 39% of the patients (50% of the PT). Even though the burden of life-long treatment must be taken into account, the similarities of effects in the patients previously treated with ablative treatment and those not treated on both GH/IGF-I suppression and tumor size reduction suggest a role for LAN60 in the primary treatment of acromegaly, at least in some group of patients with a low rate of cure after NS (elderly, large/invasive tumors). The recent development of a new formulation of LAN, namely Autogel, which is claimed to have better bioavailability and a more prolonged duration of action (51), will perhaps further improve our efforts against this disease.

Acknowledgments

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