Efficacy of the new long-acting formulation of lanreotide (Lanreotide Autogel) in somatostatin analogue-naive patients with acromegaly

G. Lombardi[1], F. Minuto[2], G. Tamburrano[3], M.R. Ambrosio[4], G. Arnaldi[5], M. Arosio[6], V. Chiarini[7], R. Cozzi[8], S. Grottoli[9], F. Mantero[10], F. Bogazzi[11], M. Terzolo[12], P. Tita[13], P.F. Boscani[14], and A. Colao[1]

[1]Department of Molecular and Clinical Endocrinology and Oncology, University Federico II of Naples, Naples; [2]Di.S.E.M. Department of Endocrinology and Metabolism, Genoa; [3]Department of Endocrinology, University of Rome "Sapienza", Policlinico Umberto I, Rome; [4]Department of Biomedical Sciences and Advanced Therapies, Unit of Endocrinology, University of Ferrara, Ferrara; [5]Department of Endocrinology, Polytechnic University of Marche, Ancona; [6]Department of Medical Sciences, University of Milan, Milan; [7]Division of Endocrinology, "Maggiore" Hospital, Bologna; [8]Division of Endocrinology, "Niguarda Cà Granda" Hospital, Milan; [9]Department of Internal Medicine, Division of Endocrinology and Metabolism, University of Turin, Turin; [10]Division of Endocrinology, Department of Surgical and Medical Sciences, University of Padua, Padua; [11]Department of Endocrinology, University of Pisa, "Cisanello" Hospital, Pisa; [12]Division of Endocrinology, "San Luigi Gonzaga" Hospital, Orbassano; [13]Division of Endocrinology, "Garibaldi" Hospital, Catania; [14]Ipsen S.p.A., Milan, Italy

ABSTRACT. ***Objective:*** **To evaluate efficacy and safety of lanreotide autogel (ATG) 120 mg injections every 4-8 weeks in somatostatin analogue-naïve patients with acromegaly.** ***Design:*** **Open, non-comparative, phase III, multicenter clinical study.** ***Methods:*** **Fifty-one patients (28 women, aged 19-78 yr): 39 newly diagnosed (*de novo*) and 12 who had previously undergone unsuccessful surgery (post-op, 11 macro and 1 micro) were studied. ATG 120 mg was initially given every 8 weeks for 24 weeks and subsequently changed according to GH levels: if ≤2.5 µg/l every 8 weeks (group A, 17 patients); if 2.5-5 µg/l every 6 weeks (group B, 15 patients); and if >5 µg/l every 4 weeks (group C, 19 patients). Treatment duration was 48-52 weeks. The primary objective was to control GH and IGF-I levels (GH≤2.5 µg/l and IGF-I normalized for age/gender). Secondary objectives were to assess GH, IGF-I, and acid-labile subunit (ALS) decrease, improvement of clinical symptoms and quality of life (QoL).** ***Results:*** **GH levels normalized in 32 patients (63%), similarly in *de novo* and post-op patients (72% *vs* 50%, *p*=0.48); in 100% of group A, in 73% of group B and in 21% of group C (*p*<0.0001). IGF-I levels normalized in 19 patients (37%), similarly in the *de novo* and post-op patients (33% *vs* 50%, *p*=0.48): in 65% of group A, 33% of group B, and in 16% of group C. Circulating GH levels decreased by 80±17%, IGF-I levels by 44±27%, and ALS by 30±17%. Symptoms (hyperhidrosis (68.6%), swelling (68.6%), asthenia (58.8%), spine arthralgia (54.9%), and paresthesias (52.9%) and QoL (from 9.1±7.9 to 6.1±6.6) significantly improved (*p*<0.001). No patient withdrew from the study because of adverse events (AE). The most frequent AE was diarrhea (76.2% of patients): at study end 16 mild and 1 moderate diarrhea were recorded. Gallstones developed in 12% of patients.** ***Conclusion:*** **ATG 120 mg in somatostatin-naïve patients with acromegaly controls GH secretion in 63% and IGF-I secretion in 37% during a 48-52 week period without any difference between *de novo* and post-op patients. The treatment was associated with improvement in clinical symptoms and QoL and with a good, safe profile.**

(J. Endocrinol. Invest. 32: 202-209, 2009)

INTRODUCTION

First-line treatment of acromegaly with surgical adenomectomy in patients with macroadenomas fails in more than 50% of patients, as defined by increased levels of GH and IGF-I and persistence of clinical symptoms (1, 2). The development of somatostatin analogues has made it possible to normalize GH and IGF-I levels and to improve clinical symptoms in most of the patients unsuccessfully operated (3). In recent years, independent studies have demonstrated beneficial effects of depot somatostatin analogues administered to newly diagnosed patients with acromegaly as first-line treatment (4).

Lanreotide is a synthetic octapeptide analogue of somatostatin, which binds preferentially to pituitary somatostatin receptors to inhibit GH secretion (5), therefore reducing IGF-I levels. Its efficacy in patients with active acromegaly was demonstrated in several clinical studies and a marketing authorization has been obtained in 52 countries world-wide for a micro-particle formulation. This first registered galenic form of lanreotide 30 mg enabled the release of the peptide over a period of 7 to 14 days after im administration.

In order to further extend the duration of the release of the active ingredient, a new formulation of lanreotide, lanreotide Autogel (ATG) 60 mg, 90 mg and 120 mg was developed. The ATG formulation consists of a solution of lanreotide in water with no additional excipients.

In a pharmacokinetic (PK) study conducted in 24 volunteers, ATG exhibited linear pharmacokinetics for the 60 to 120 mg doses and provided a prolonged dosing interval and good tolerability (6). Caron et al. (7) demon-

---

The study (A-93-52030-077) has been registered in www.clinicaltrials.gov as NCT00499993

Key-words: Acromegaly, GH, IGF-I, lanreotide, pituitary tumors.

Correspondence: G. Lombardi, MD, PhD, Department of Molecular and Clinical Endocrinology and Oncology, "Federico II" University of Naples, via S. Pansini 5, 80131 Naples, Italy.

E-mail: gaelomba@unina.it

Accepted May 7, 2008.

strated that the micro-particle lanreotide and the ATG have equal efficacy, and proposed equivalent doses of the two formulations. Lucas et al. (8) have confirmed these results in a large multicenter trial. Efficacy of ATG was reported up to 3 yr from treatment (9). Other studies have subsequently demonstrated that ATG was as effective as octreotide-long acting release (LAR) in patients with acromegaly (10-12).

Since data on the efficacy of ATG in patients with acromegaly are still limited (13), the current study was designed to assess efficacy and safety profile of ATG120 mg administered every 4 to 8 weeks for 12 months in somatostatin analogue-naive patients.

MATERIALS AND METHODS

Study design

This is an open, non-comparative, phase III, multicenter clinical study.

Objectives

The primary objective was to evaluate the efficacy of the ATG 120 mg on control of GH and IGF-I excess in acromegaly according to the currently accepted criteria (14). The secondary objectives were to assess decrease of GH, IGF-I, and acid-labile subunit (ALS) levels, improvement of clinical symptoms and QoL and safety profile.

Inclusion criteria

Patients aged ≥18 yr with active acromegaly [serum GH levels above 5 µg/l and/or above 1 µg/l after oral glucose tolerance test (OGTT) and abnormal IGF-I values], who signed the written informed consent form. Patients should not have undergone pituitary surgery less than 3 months before selection, somatostatin analogues (except for a pre-surgical treatment of less than 3 months) or radiotherapy.

Exclusion criteria

Patients who had undergone pituitary surgery less than 3 months before selection or previously treated with radiotherapy or previously treated with a somatostatin analogue for longer than 3 months or previously treated with a dopamine agonist (for a period >3 months and interrupted <6 months before selection) or requiring such treatment during the study. Patients suffering from active malignant disease, except basocellular carcinoma of the skin or *in situ* carcinoma of the uterine cervix. Women at risk of pregnancy during the study, not consenting to take adequate precautions against pregnancy. Pregnant or breast-feeding patients. Patients who had known hypersensitivity to any of the test materials or related compounds. Patients receiving any unlicensed drug within the previous 30 days or scheduled to receive any unlicensed drug other than ATG during the course of the study. Patients with evidence of drug/alcohol abuse. Patients unable or unwilling to fully comply with the protocol.

Determination of sample size

The determination of sample size was made using nQuery procedures and assuming a rate of patients with normalized GH levels at study end of at least 20% (minimum acceptable response rate) to 40% (minimum relevant clinical rate). With a type I error =0.05 (1-sided) and 90% power, the sample size required was of 54 patients.

Patients

Twenty-four centers participated in the study coordinated by G. Lombardi (University "Federico II", Naples, Italy). The inclusion of a minimum of 2 patients (at least 1 newly diagnosed) was required at each center. The study was approved by the Ethics Committees of all Centers. Patients gave their written informed consent prior to entering the study. The study was performed according to the principles defined by the declaration of Helsinki (1964) and subsequent modifications and in compliance with Good Clinical Practice (GCP).

Of 64 patients screened, 1 was excluded since the adenoma spontaneously melted between selection and baseline visit. He never took the study drug and was excluded from the statistical analysis. Of the remaining 63 patients, 4 dropped out before week 16 and therefore were not assigned to any treatment subgroup and 8 patients dropped out between week 16 and the final visit; 1 of 8 withdrew his consent to take part in the study.

Thus, the study population consists of 51 patients, 28 women and 23 men, aged 19-78 yr (median 50 yr). Fasting baseline GH levels (mean of 5 samples of a diurnal profile) were 19.4±21.3 µg/l (median 10.3 µg/l) and IGF-I levels were 703.4±274.2 µg/l (median 697 µg/l). IGF-I levels proved to be 2.5 times (median) above the upper limit of normal range (ULN) according to age- and sex-normative data. On magnetic resonance imaging (MRI), 30 patients had macroadenomas, 19 had microadenomas, and 2 had empty sella. Of the 51 patients, 39 were newly diagnosed (*de novo*) and 12 had previously undergone unsuccessful surgery (post-op, 11 macro and 1 micro). Table 1 shows the characteristics of the 2 groups at study entry.

Safety population

The safety population, as defined by the protocol, consists of patients who received at least 1 study drug dosing and includes 63 patients.

Hormonal evaluation

GH levels were assessed as a mean value of 5 samples at 30-min intervals (starting between 08:00 and 09:00 h) taken at each visit before the injection of ATG. At inclusion (V0) and at final visit, GH concentrations after OGTT were also determined (data not shown). IGF-I and ALS levels were assessed as a single sample taken at each visit at the same time as the first GH sample. All hormonal parameters were assessed in a central laboratory (D.i.S.E.M. – University of Genoa).

Table 1 - *Patients' profile at study entry. Patients are classified as newly diagnosed (*de novo*) or as having already undergone unsuccessful surgery (post-op).*

	De novo	Post-op	*p*
No.	39	12	
Women/Men	21/18	7/5	0.85
Macroadenomas	19	11	0.03
Microadenomas	18	1	0.03
Empty sella	2	0	0.03
Age (yr)	53±14	40±12	0.008
Baseline GH levels (µg/l)	17.8±20.0	24.8±25.3	0.28
Nadir GH levels (µg/l)	2.7±3.8	3.0±2.6	0.51
GH suppression (%)	79.5±17.6	80.8±15.5	1.0
Baseline IGF-I levels (µg/l)	736.9±273.4	678.3±309.7	0.65
Nadir IGF-I levels (µg/l)	360.5±164.8	438.5±259.3	0.54
IGF-I suppression (%)	47.8±26.7	32.7±26.1	0.053

p-values for continuous variables were calculated with the Mann-Whitney test. *p*-values for categorical variables were calculated with the Chi-square test.

Study protocol

ATG120 mg was given as a deep sc injection into the buttock. Once all baseline assessments had been performed, each patient received one deep sc injection of ATG 120 mg at Visit 1 (V1) and then a subsequent injection every 8 weeks for a total of 3 injections (period 1). Then, on the basis of GH levels (mean of 5 samplings at 30-min intervals) as measured at V3, the dosing interval was determined as follows (period 2): if GH levels were ≤2.5 µg/l ATG 120 mg was maintained every 8 weeks for another 3 injections (group A); if GH levels were between 2.5-5 µg/l, ATG 120 mg was given every 6 weeks for another 4 injections (group B); if GH levels were >5 µg/l, ATG 120 mg was given every 4 weeks for another 7 injections (group C). The duration of treatment was 48-52 weeks. In this study we report the results obtained before starting ATG treatment and the lowest GH and IGF-I level (nadir) measured after ATG treatment (Fig. 1).

Criteria for evaluation

Efficacy

We considered controlled the patients achieving GH levels as mean of 5 samples in a diurnal profile ≤2.5 µg/l in the presence of IGF-I levels normalized for age and gender. Improvement in clinical symptoms was considered on the basis of a semiquantitative scale for asthenia, hyperhidrosis, headache, swelling of extremities, arthralgia, paresthesia, carpal tunnel syndrome: symptoms were graded as 0= absent, 1= mild, 2= moderate, 3= severe. The Nottingham questionnaire was used at visit 1 and at the final visit of the study it was used to measure quality of life (QoL).

Safety

Any adverse event (AE) during the study was monitored and reported by the investigators. Safety, evaluated by local laboratory data, was assessed at inclusion and at the final visit by: hematology: erythrocytes, leukocytes, platelets, hemoglobin, hematocrit; biochemistry: glucose, creatinine, alkaline phosphatase, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), electrolytes (sodium, potassium, calcium, phosphorous), glycosylated hemoglobin, triglycerides, total and HDL cholesterol, blood amylase, sideremia, transferrin, prothrombin; glucose and insulin concentrations after OGTT; hormonal evaluation: TSH, free T_3 (FT_3), free T_4 (FT_4), FSH, and LH levels. Safety related to gallbladder was assessed by ultrasound examination performed at inclusion and at the end of the study.

Methods

Serum samples for GH, IGF-I, and ALS measurements were collected in fasting conditions and stored at –20 C until shipping to the central lab. GH was measured by a chemiluminescent immunoradiometric assay (Immulite, DPC, Los Angeles, CA, USA). The analytical sensitivity of this assay was 0.01 µg/l, standard curve was calibrated against WHO 1st IRP 80/505 (1 mg=2.6 IU). IGF-I was measured by radioimmunoassay using immunochemicals and tracer provided by Biosource (Nivelles, Belgium). The assay sensitivity was 150 pg/ml (1.2 nmol/l). To avoid interference from binding proteins, single plasma EDTA were treated with acid ethanol. The values were compared with an appropriate age-adjusted range as follows (3^{rd}-97^{th} percentile): 20-29 yr: 76-389; 30-39: 60-353; 40-49: 68-266; 50-59: 62-252; 60-65: 40-217.5; 66-75: 40-209 µg/l.

Total ALS was measured by specific two-site sandwich enzyme-linked immuno-sorbent assay, using anti-ALS antibodies raised against synthetic amino-terminal and carboxyl-terminal ALS peptides, and reagents and tracer provided by Diagnostics Systems Laboratories, Inc. (Webster, TX). All samples were pretreated to dissociate the complexed ALS and enhance ALS immuno-reactivity. The sensitivity of the assay was 4.7 nmol/l; the intra- and inter-assay coefficients of variation were 5.5% and 7.2%, respectively. Recovery of human serum-derived glycosilated ALS, purified as previously described (15), was 75% for the lower concentration added (1 µg) and 95% for the higher concentration added (60 µg). The values were compared with an appropriate age-adjusted range (3^{rd}-97^{th} percentile) obtained by the same laboratory in a large group of healthy subjects as follows: 20-29 yr =19.4-29.8, 30-39 yr =19.6-29.9, 40-49 yr =18.3-29.7, 50-59 yr =18.3-28.0, >65 yr 18.3-25.5 µg/l.

All hematological and biochemical tests, including thyroid function, glucose and insulin, were locally measured by routine assays.

Statistical methods

The primary efficacy analysis was based on the per protocol population (51 patients). The assessment of safety was based on the safety population (63 patients). The primary efficacy analysis assessed the percentage and its 95% confidence interval (CI) of patients with normalized GH levels, considered as mean GH value of 5 samples over 2 hours ≤2.5 µg/l. Comparison between *de novo* and post-op patients was performed by the Mann-Whitney test. Comparison among treatments groups A, B, and C was performed by the Kruskal-Wallis test followed by the Dunn's

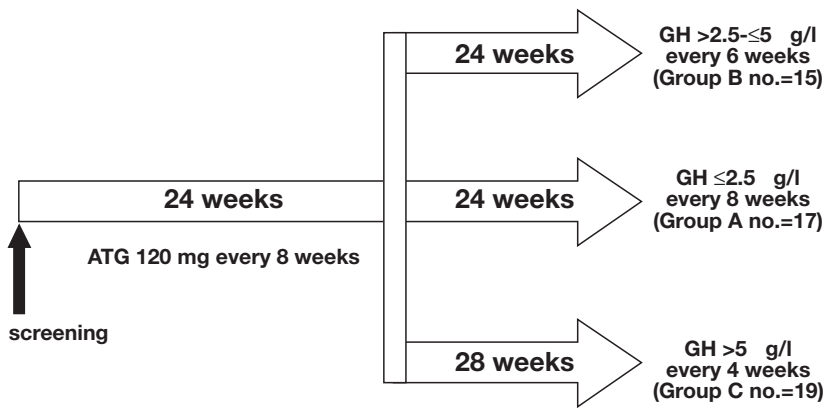

Fig. 1 - *Summary of the study protocol. ATG: lanreotide autogel.*

multiple comparison test. Differences in clinical symptoms were analyzed by the Mc Nemar test. A two-side *p*-value <5% was taken as statistically significant. Safety data were summarized by descriptive statistics before and after ATG treatment. No inferential statistical tests were performed.

RESULTS

Post-op patients were significantly younger and had a higher prevalence of macroadenomas than the *de novo* ones (Table 1). The patients enrolled in groups A and B were older and had lower GH (only group A) and IGF-I levels at baseline than those of group C (Table 2).

Primary objective

Nadir GH levels normalized in 32 out of 51 (63%) patients similarly in *de novo* and in post-op patients [26/39 (72%) *vs* 6/12 (50%), p=0.48] and in females and in males [17/28 (61%) *vs* 15/23 (65%), p=0.97]. GH levels normalized in all 17 patients of group A (100%), 11 of 15 patients of group B (73%) and in 4 of 19 patients of group C (21%; p<0.0001). IGF-I levels normalized in 19 out of 51 (37%) patients, similarly in *de novo* and post-op patients [13/39 (33%) and 6/12 (50%); p=0.48]. IGF-I levels normalized in 11 of 17 patients of group A (65%), 5 of 15 patients of group B (33%) and in 3 of 19 patients of group C (16%). Of the 19 patients with normalized IGF-I levels only 1 had unsuppressed GH levels (a 26-yr-old woman with a post-op macroadenoma and a nadir GH of 5 µg/l). Of the remaining 14 patients with normalized GH levels, 4 (28%) had near-normal IGF-I levels (1.01-1.3 times above the upper limit of normal range).

Secondary objectives

Serum GH and IGF-I levels

Mean GH level decreased from 19.4±21.3 µg/l at study entry, to 7.0±6.8 µg/l at week 8 and 4.5±4.9 µg/l at the final visit (p<0.0001). Percentage of GH suppression was 80±17%. Figure 2 shows the individual GH levels before and after treatment, according to the different treatment schedules (group A, B, and C). Similarly, mean IGF-I level decreased from 703.4±274.2 µg/l at study entry, to 526±264 µg/l at week 8 and 455.4±227.9 µg/l at the final visit (p<0.0001). Percentage of IGF-I suppression was 44±27%. Figure 3 shows the individual IGF-I levels before and after treatment, according to the different treatment schedules (group A, B, and C). Nadir GH and IGF-I levels during ATG treatment in the patients enrolled in groups A and B were significantly lower than those observed in the patients of group C (Table 2).

ALS levels

The greatest decrease of ALS was also noticed on the first visit after the treatment start, from 55.6±19.4 µg/ml at week 0, to 45.1±18.9 µg/ml at week 8. At the final visit the ALS level was 38.8±15.8 µg/ml (p<0.001). Percent ALS suppression was 30±17%. ALS was significantly higher in the patients of group C than in those of group A, in accordance with the results of IGF-I levels (Table 2). At treatment end, ALS levels were decreased in all treatment groups: in patients of group A and B ALS levels were significantly lower than in patients of group C (Table 2).

Symptoms of acromegaly

The prevalence of symptoms at baseline and final visits is summarized in Table 3. The most frequent symptoms at baseline were hyperhidrosis (68.6%), swelling sensation (68.6%), asthenia (58.8%), arthralgia of the spine (54.9%), and paresthesias (52.9%). Those symptoms disappeared in most patients after treatment (Table 3). The Mc Nemar test confirmed a significant decrease of all symptoms but two, namely arthralgia of the shoulder and arthralgia of the pelvis, which affected a small number of patients.

Quality of life: Nottingham Questionnaire

The QoL score, calculated as the sum of the disturbances by the Nottingham Questionnaire, was 9.1±7.9 at the first visit and decreased to 6.1±6.6 at the final visit. The changes in single individuals at the end were –2 in median (–2.8±4.6) and were statistically significant at the Wilcoxon Signed Ranks test (p<0.001) (Table 4).

Safety

In the safety population the average treatment duration was 266.5±75.5 days (median 282 days). No patient withdrew from the study because of AE. Three serious AE were reported in 2 patients during the study: a male of 60 yr experienced diarrhea, considered to be probably

Table 2 - *Characteristics of the patients enrolled in group A (lanreotide-autogel 120 mg injections every 8 weeks), group B (lanreotide-autogel 120 mg injections every 6 weeks) and group C (lanreotide-autogel 120 mg injections every 4 weeks).*

	Group A	Group B	Group C	*p*
No.	17	15	19	
Women/Men	10/7	8/7	10/9	0.92
De novo/Post-op	13/4	12/3	14/5	0.86
Age (yr)	59±12[a]	52±13[b]	39±11	0.0003
Baseline GH levels (µg/l)	9.2±12.6[a]	16.9±19.0	30.5±24.7	<0.001
Nadir GH levels (µg/l)	0.8±0.4[a]	1.9±1.2[b]	5.1±4.1	<0.001
GH suppression (%)	84.5±10.5	78.7±17.3	76.6±20.9	0.57
Baseline IGF-I levels (µg/l)	594±279[a]	635±178[b]	855±275	0.0021
Nadir IGF-I levels (µg/l)	255±123[a]	347±140[b]	515±195	<0.001
IGF-I suppression (%)	53.3±25.8	39.5±33.4	39.9±21.3	0.15
Baseline ALS levels (µg/l)	45.6±15.0[a]	57.2±17.9	63.5±20.6	0.017
Nadir ALS levels (µg/l)	31.8±13.5[a]	35.7±12.3[b]	47.5±16.8	0.006

p-values for continuous variables were calculated with the Kruskal-Wallis test followed by Dunn's multiple comparison test. p-values for categorical variables were calculated with the Chi-square test. [a]p<0.01 *vs* C; [b]p<0.05 *vs* C. Patients are classified as newly diagnosed (*de novo*) or as having already undergone unsuccessful surgery (post-op). ALS: acid-labile subunit.

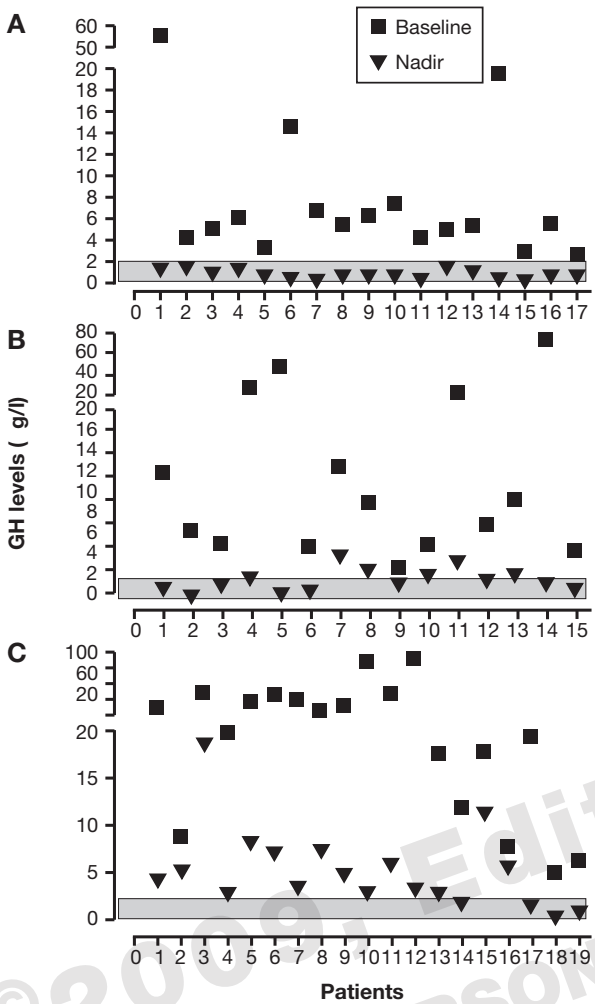

Fig. 2 - *Individual results of serum GH levels before and after treatment with lanreotide autogel 120 mg every 56 days (A), every 42 days (B) or every 28 days (C). The grey area corresponds to the normal GH levels (≤2.5 µg/l).*

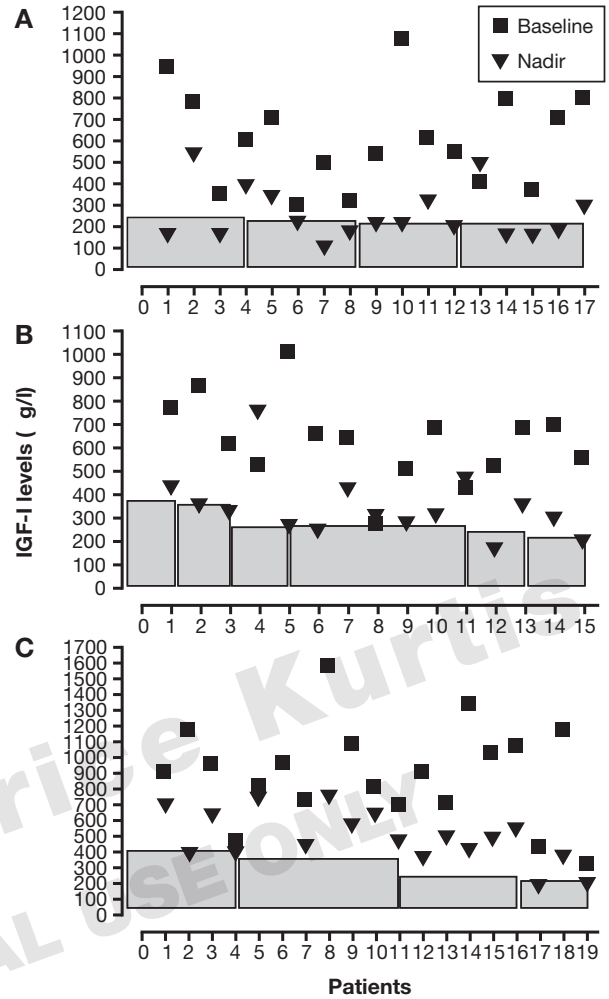

Fig. 3 - *Individual results of serum IGF-I levels before and after treatment with lanreotide autogel 120 mg every 56 days (A), every 42 days (B) or every 28 days (C). The grey area corresponds to the normal IGF-I levels for age, as reported in the Methods section.*

related to study treatment and dyspnea due to atrial fibrillation and judged as unrelated to treatment; a woman of 65 yr was admitted to hospital due to hypercortisoluria classified as unrelated to treatment. Overall, during the trial 60 out of the 63 patients complained of AE. The most frequent AE was diarrhea, reported by 48/63 patients (76.2%). At the final visit 16 mild and 1 moderate diarrhea were recorded in 33.3% of patients. Pain and induration at the injection site were reported in 27 patients (42.9%) and abdominal pain was reported by 36 patients (57.1%). Nausea was not frequent and mostly mild to moderate; severe nausea was reported by 1 patient. Vomiting was rare, severe in 1 patient. Abdominal cramps were less frequent during the early treatment phase (Table 5).

Data on gallbladder ultrasonography both at baseline and at the final visit were available in 50 patients. Out of these, 2 patients (4%) had gallstones from the beginning to the end of the study, and 6 (12%) developed gallstones during the study period (Table 5).

DISCUSSION

The results of the present study demonstrate that ATG 120 mg treatment at different intervals between injections normalized GH and IGF-I levels in 63% and 37% of somatostatin-naive patients with active acromegaly, respectively. No difference was found in the outcome of ATG 120 mg in *de novo* and post-op patients, thus confirming previous results (16-19). A delayed interval between injections as long as 56 days was successful in 17 of 51 patients (33.3%) while in 19 patients (37.2%) the interval was shortened to 28 days, which is similar to that commonly used in patients treated with octreotide-LAR. Intermediate intervals between injections of 42 days was used in the remaining 15 patients (29.4%). As expected, shortening the interval between injections (that corresponds to an increase in the final ATG dosage) was followed by a lower success rate in terms of GH and IGF-I normalization, indicating that the patients treated in this study with ATG 120 mg every 28 days are less responsive

Table 3 - *Rate of patients with symptoms of acromegaly.*

	Baseline visit		Final visit		Delta	*p*
	No.	(%)	No.	(%)	(%)	
Hyperhidrosis	35	68.6	14	27.5	–41.2%	<0.001
Swelling sensation	35	68.6	14	27.5	–41.2%	<0.001
Asthenia	30	58.8	19	37.3	–21.6%	0.008
Arthralgia of the spine	28	54.9	16	31.4	–23.5%	0.001
Paresthesias	27	52.9	10	19.6	–33.3%	<0.001
Arthralgia of the extremities	22	43.1	10	19.6	–23.5%	0.001
Headache	21	41.2	11	21.6	–19.6%	0.007
Arthralgia of the knees	19	37.3	10	19.6	–17.6%	0.003
Arthralgia of the shoulder	13	25.5	7	13.7	–11.8%	0.053
Arthralgia of the pelvis	10	19.6	7	13.7	–5.9%	0.257
Carpal tunnel syndrome	10	19.6	3	5.9	–13.7%	0.008

p-values refer to the Mc Nemar Test results.

to the treatment (20). A similar finding has already been documented in patients treated with octreotide-LAR at dosages of 30 to 40 mg every 28 days (17). ATG 120 mg treatment was associated with significant improvement of clinical symptoms and QoL and was found to have a safety profile similar to other somatostatin analogues.

Up to now, no studies have reported the efficacy of ATG treatment in newly diagnosed or in somatostatin analogue-naive patients with acromegaly. Caron et al. (7, 9) previously reported that the ATG formulation had an efficacy similar to that observed with the old lanreotide slow release (SR) formulation as confirmed by Lucas et al. (8). Dose equivalence was also proposed as ATG 60 mg, 90 mg, and 120 mg every 28 days are equivalent to lanreotide SR 30 mg every 14 days, 10 days and 7 days, respectively. Subsequent studies reported that the ATG formulation had similar efficacy to octreotide-LAR (10-12). Overall, 55 patients were reported after both LAR and ATG at different dosages and after a wash out period: all three studies demonstrated that GH and IGF-I levels were similar with either drug (10-12).

In the current study, we investigated for the first time a large population of 51 patients who had never previously received treatment with somatostatin analogues. The majority of the patients enrolled in the study were newly diagnosed (76.5%) while only a minority were enrolled after unsuccessful surgery (23.5%). Normalization of GH and IGF-I secretion did not differ in the 2 patient groups, in line with previous findings (16-19). It is worth noting that ATG 120 mg was successful in two thirds of the patients even when injected with a 42-to 56-day interval between injection. Indeed, control of GH excess was achieved in 100% and 73%, respectively, and age-normalization of IGF-I levels in 65% and 33%, respectively, in patients treated every 56 and 42 days for 48 weeks. The prolonged interval between injections may improve the patients' compliance to the long-term treatment: this issue was, however, not evaluated in detail in the current study. The outcome of ATG 120 mg given every 28 days could be considered disappointing since only 21% and 16% of 19 patients achieved control of GH and IGF-I levels, respectively. It should be considered, however, that shortening of the interval between injections was allowed for the second part of the study and was thus limited to 24 weeks only. Therefore, the possibility that prolonged treatment with a 28-day interval could induce further benefit in terms of GH and IGF-I levels cannot be ruled out from the current study. On the other hand, Cozzi et al. (21) have demonstrated that prolonged treatment with octreotide-LAR in-

Table 4 - *Descriptive statistics for Nottingham Questionnaire.*

	Group A	Group B	Group C	*p*	Total
No.	17	15	19		51
Baseline	11.1±8.1	10.0±9.8	6.7±5.5	0.22	9.1±7.9
Post-treatment	7.1±6.3	6.6±8.0	4.9±5.8	0.87	6.1±6.6
p					<0.001

p-values refer to the Wilcoxon Signed Ranks test.

Table 5 - *International classification of diseases,10th revision (ICD10 classification), of adverse events.*

	Patients	
	No.	%
Not infective enteritis and colitis (diarrhea)	48	76.2
Abdominal pain	36	57.1
Pain or induration at the injection site	27	42.9
Arthropathy due to endocrine/nutritional/metabolic diseases	24	38.1
Headache	20	31.7
Nausea and vomiting	16	25.4
Malaise and asthenia	11	17.5
Flatulence and related conditions	9	14.3
Cutaneous paresthesia	9	14.3
Gallbladder stone without cholecystitis	8	12.7
Abdominal pain, upper	6	9.5
Hyperhidrosis	6	9.5
Fever	5	7.9
Pruritus	4	6.3
Alopecia without skin scars	3	4.8
Constipation	3	4.8
Periapical dental abscess without fistula	3	4.8
Renal colic	3	4.8

duced a progressive control of GH and IGF-I during a 9-yr follow-up. Based on the similarities between octreotide-LAR and ATG (10-12) which have been recently reviewed by Murray and Melmed (22), long-term treatment with ATG could be followed by progressive control of GH and IGF-I levels and further studies are required to confirm this hypothesis.

In the current study, we also investigated the change in ALS levels after ATG 120 mg treatment. It has been suggested that ALS, the main component of the circulating 150k-Da complex might be a good marker to reflect integrated GH secretion. Previous studies demonstrated that ALS levels are reduced to normal levels after successful surgery and radiotherapy (23-25). A recent study failed to reveal normalization of ALS levels during ATG 120 mg treatment (26). It should be noted, however, that Ronchi et al. did investigate patients already treated with octreotide-LAR and that changes in ALS levels might also depend on direct effects of somatostatin analogues (26). We found that ALS levels nicely followed GH and IGF-I reduction in the 51 patients: in fact, in patients of group A and B, who had a greater response in terms of GH and IGF-I than those of group C, ALS levels were significantly lowered by ATG treatment.

The analysis of the clinical symptoms and of the questionnaire on the QoL also supported the results of GH and IGF-I measurements. In fact, most of the clinical symptoms, with the sole exception of arthralgias of pelvis and shoulder, improved significantly in this cohort. At the time of the study, a specific questionnaire to assess QoL in acromegaly was not available as it currently is (27). Nevertheless, a significant improvement in the Nottingham questionnaire was found in all patients. Even when grouped according with the different treatment schedules, a significant improvement of QoL remains and no difference was found among groups. These data are particularly useful in consideration of the many systemic complications that characterize acromegaly (28).

Lastly, ATG 120 mg was tolerated well by the patients and none of the 63 patients enrolled in the study withdrew from treatment because of side effects. The safety profile was very similar to the well-known profile of somatostatin analogues, with gastrointestinal disturbances being the most frequent complaints (3). Generally, however, disturbances subside spontaneously with treatment continuation. New gallstones were documented in 12%.

CONCLUSION

Lanreotide autogel 120 mg given to somatostatin-naïve patients with acromegaly at different injection intervals of 28, 42 or 56 days induce control of GH secretion in 63% and of IGF-I secretion in 37% during a 48-52 week treatment period. No difference in treatment outcome was observed between newly diagnosed and post-surgery patients. The treatment was also associated with improvement in clinical symptoms and QoL with a good safe profile. These data, together with the new findings demonstrating significant tumor shrinkage of GH-secreting adenomas in newly diagnosed patients treated with lanreotide-Autogel (29), reinforce the use of somatostatin analogues as first-line treatment of acromegaly, as recently suggested (30).

ACKNOWLEDGMENTS

The study was sponsored by Ipsen (Italy). The Italian Multicenter Autogel Study Group in Acromegaly comprises:
R. Baldelli (Department of Endocrinology, University "La Sapienza" Policlinico Umberto I, Rome, Italy); A. Barreca† and M. Giusti (Di.S.E.M. Department of Endocrinology and Metabolism, Genoa); P. Beck-Peccoz and C. Ronchi (Department of Medical Sciences, University of Milan, Milan, Italy); M. Boscaro (Department of Endocrinology, Polytechnic University of Marche, Ancona, Italy); F. Cavagnini and L. Fatti (Istituto Auxologico Italiano, "San Luca" Hospital, Milan, Italy); N. Cremonini (Division of Endocrinology "Maggiore" Hospital, Bologna, Italy); L. De Marinis (Division of Endocrinology, "Agostino Gemelli" Hospital, Catholic University, Rome, Italy); E. De Menis and B. Roiter (Service of Endocrinology, Cà Foncello Hospital, Treviso, Italy); E. degli Uberti and M. Bondanelli (Department of Biomedical Sciences and Advanced Therapies, Unit of Endocrinology, University of Ferrara, Ferrara, Italy); G. Delitala and G. Fanciulli (Department of Internal Medicine, University of Sassari, Sassari, Italy); E. Martino and M. Gasperi (Department of Endocrinology, University of Pisa, "Cisanello" Hospital, Pisa, Italy); E. Ghigo and V. Gasco (Department of Internal Medicine, Division of Endocrinology and Metabolism, University of Turin, Turin, Italy); A. Giustina and S. Bonadonna (Endocrinology Unit, "Spedali Civili" Hospital, Brescia, Italy); F. Grimaldi (Endocrinology Unit, Azienda Ospedaliero-Universitaria, Udine, Italy); P. Loli (Division of Endocrinology, "Niguarda Cà Granda" Hospital, Milan, Italy); S. Mariotti and F. Pigliaru (Institute of Endocrinology, Department of Medical Sciences, University of Cagliari, Policlinico Monserrato, Cagliari, Italy); G. Pagani and M. Montini (Endocrinology Unit, "Ospedali Riuniti" Hospital, Bergamo, Italy); A. Paoletta (Division of Endocrinology, Department of Surgical and Medical Sciences, University of Padua, Padua, Italy); V. Pezzino (Division of Endocrinology, "Garibaldi" Hospital, Catania, Italy); R. Pivonello and R.S. Auriemma (Department of Molecular and Clinical Endocrinology and Oncology, University Federico II of Naples, Naples, Italy); G. Reimondo (Division of Endocrinology, "San Luigi Gonzaga" Hospital, Orbassano, Italy); F. Rosato (Division of Endocrinology, "V Cervello" Hospital, Palermo, Italy); F. Santeusanio and G. Angeletti (University of Perugia, Perugia, Italy); M. Serio and M. Mannelli (Department of Clinical Physiopathology, University of Florence, Florence, Italy); R. Valcavi and M. Pesenti (Unit of Endocrinology, Arcispedale S. Maria Nuova, Reggio Emilia, Italy).

REFERENCES

1. Melmed S, Casanueva FF, Cavagnini F, et al; Acromegaly Treatment Consensus Workshop Participants. Guidelines for Acromegaly Management. J Clin Endocrinol Metab 2002, 87: 4054-8.
2. Colao A, Lombardi G. Growth-hormone and prolactin excess. Lancet 1998, 352: 1455-61.
3. Freda PU. Somatostatin analogs in acromegaly. J Clin Endocrinol Metab 2002, 87: 3013-8.
4. Sheppard MC. Primary medical therapy for acromegaly. Clin Endocrinol (Oxf) 2003, 58: 387-99.
5. Heiman ML, Murphy WA, Coy DH. Differential binding of somatostatin agonists to somatostatin receptors in brain and in adenohypophysis. Neuroendocrinology 1987, 45: 429-36.
6. Antonijoan RM, Barbanoj MJ, Cordero JA, et al. Pharmacokinetics of a new Autogel formulation of the somatostatin analogue lanreotide after a single subcutaneous dose in healthy volunteers. J Pharm Pharmacol 2004, 56: 471-6.
7. Caron P, Beckers A, Cullen DR, et al. Efficacy of the new long-acting formulation of lanreotide (lanreotide Autogel) in the management of acromegaly. J Clin Endocrinol Metab 2002, 87: 99-104.
8. Lucas T, Astorga R; Spanish-Portuguese Multicentre Autogel Study Group on Acromegaly. Efficacy of lanreotide Autogel administered every 4-8 weeks in patients with acromegaly previously responsive to lanreotide microparticles 30 mg: a phase III trial. Clin Endocrinol (Oxf) 2006, 65: 320-6.
9. Caron P, Cogne M, Raingeard I, Bex-Bachellerie V, Kuhn JM. Effectiveness and tolerability of 3-year lanreotide Autogel treatment in patients with acromegaly. Clin Endocrinol (Oxf) 2006, 64: 209-14.
10. Ashwell SG, Bevan JS, Edwards OM, et al. The efficacy and safety of lanreotide Autogel in patients with acromegaly previously treated with octreotide LAR. Eur J Endocrinol 2004, 150: 473-80.

11. Alexopoulou O, Abrams P, Verhelst J, et al. Efficacy and tolerability of lanreotide Autogel therapy in acromegalic patients previously treated with octreotide LAR. Eur J Endocrinol 2004, 151: 317-24.
12. Van Thiel SW, Romijn JA, Biermasz NR, et al. Octreotide long-acting repeatable and lanreotide Autogel are equally effective in controlling growth hormone secretion in acromegalic patients. Eur J Endocrinol 2004, 150: 489-95.
13. Ciccarelli A, Daly A, Beckers A. Lanreotide Autogel for Acromegaly. A new addition to the treatment armamentarium. Treat Endocrinol 2004, 3: 77-81.
14. Giustina A, Barkan A, Casanueva FF, et al. Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 2000, 85: 526-9.
15. Barreca A, Ponzani P, Arvigo M, Giordano G, Minuto F. Effect of the acid-labile subunit on the binding of insulin-like growth factor (IGF)-binding protein-3 to [125I]IGF-I. J Clin Endocrinol Metab 1995, 80: 1318-24.
16. Newman CB, Melmed S, George A, et al. Octreotide as primary therapy for acromegaly. J Clin Endocrinol Metab 1998, 83: 3034-40.
17. Colao A, Ferone D, Marzullo P, et al. Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. J Clin Endocrinol Metab 2001, 86: 2779-86.
18. Baldelli R, Colao A, Razzore P, et al. Two-year follow-up of acromegalic patients treated with slow release lanreotide (30 mg). J Clin Endocrinol Metab 2000, 85: 4099-103.
19. Ayuk J, Stewart SE, Stewart PM, Sheppard MC; European Sandostatin LAR Group. Efficacy of Sandostatin LAR (long-acting somatostatin analogue) is similar in patients with untreated acromegaly and in those previously treated with surgery and/or radiotherapy. Clin Endocrinol (Oxf) 2004, 60: 375-81.
20. Freda PU, Katznelson L, van der Lely AJ, Reyes CM, Zhao S, Rabinowitz D. Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. J Clin Endocrinol Metab 2005, 90: 4465-73.
21. Cozzi R, Montini M, Attanasio R, et al. Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective study of its efficacy in the control of disease activity and tumor shrinkage. J Clin Endocrinol Metab 2006, 91: 1397-403.
22. Murray RD, Melmed S. A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. J Clin Endocrinol Metab 2008, 93: 2957-68.
23. Arosio M, Garrone S, Bruzzi P, Faglia G, Barreca A. Diagnostic value of the acid-labile subunit in acromegaly: evaluation in comparison with insulin-like growth factor (IGF) I, and IGF-binding protein-1, -2, and -3. J Clin Endocrinol Metab 2001, 86: 1091-8.
24. Epaminonda P, Porretti S, Cappiello V, Beck-Peccoz P, Faglia G, Arosio M. Efficacy of radiotherapy in normalizing serum IGF-I, acid-labile subunit (ALS) and IGFBP-3 levels in acromegaly. Clin Endocrinol (Oxf) 2001, 55: 183-9.
25. Feelders RA, Bidlingmaier M, Strasburger CJ, et al. Postoperative evaluation of patients with acromegaly: clinical significance and timing of oral glucose tolerance testing and measurement of (free) insulin-like growth factor I, acid-labile subunit, and growth hormone-binding protein levels. J Clin Endocrinol Metab 2005, 90: 6480-9.
26. Ronchi CL, Boschetti M, Degli Uberti EC, et al.; Italian Multicenter Autogel Study Group In Acromegaly. Efficacy of a slow-release formulation of lanreotide (autogel® 120 mg) in patients with acromegaly previously treated with octreotide LAR: an open, multicenter longitudinal study. Clin Endocrinol (Oxf) 2007, 67: 512-9.
27. Webb SM, Badia X, Surinach NL; Spanish AcroQol Study Group. Validity and clinical applicability of the acromegaly quality of life questionnaire, AcroQoL: a 6-month prospective study. Eur J Endocrinol 2006, 155: 269-77.
28. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev 2004, 25: 102-52.
29. Colao A, Auriemma RS, Rebora A, et al. Significant tumour shrinkage after 12 months of Lanreotide Autogel-120 mg treatment given first-line in acromegaly. Clin Endocrinol (Oxf) 2008 Dec 15. [Epub ahead of print], doi: 10.1111/j.1365-2265.2008.03503.x
30. Colao A, Martino E, Cappabianca P, Cozzi R, Scanarini M, Ghigo E; A.L.I.C.E. Study Group. First-line therapy of acromegaly: a statement of the A.L.I.C.E. (Acromegaly primary medical treatment Learning and Improvement with Continuous Medical Education) Study Group. J Endocrinol Invest 2006, 29: 1017-20.