Context: Increase in drug frequency or dose is recommended for acromegaly patients with partial response to long-acting somatostatin receptor ligands (SRLs). However, the efficacy and safety data with lanreotide (LAN) Autogel (LAN-ATG) at high dose (HD) or high frequency (HF) are still scanty.

Objective: To evaluate the biochemical efficacy and safety of HF and HD LAN-ATG in patients with active acromegaly.

Design: Twenty-four-week prospective, multicenter, randomized, open-label trial.

Patients and Interventions: Thirty patients with active acromegaly, partial responders to SRLs, were randomized to HF (120 mg/21 days; 15 patients) or HD (180 mg/28 days; 15 patients) LAN-ATG.

Outcomes: Normalization of serum insulin-like growth factor-I (IGF-I) and reduction in random growth hormone (GH) values, 1.0 μg/L, reduction in serum IGF-I and GH from baseline, differences in biochemical response between HF and HD LAN-ATG, adverse events.

Results: IGF-I decreased significantly (P = 0.007) during the 24-week treatment, with greater decrease in HD (P = 0.03) vs HF group (P = 0.08). Normalization in IGF-I values occurred in 27.6% of patients (P = 0.016 vs baseline), without a significant difference between HF and HD groups (P = 0.59). The decrease in serum IGF-I significantly correlated with serum LAN values (P = 0.04), and normalization of IGF-I was predicted by baseline IGF-I values (P = 0.02). Serum GH values did not change significantly (P = 0.22).

Overall, 19 patients (63.3%) experienced adverse events, all being mild to moderate and transient, without differences between the two therapeutic arms.

Conclusion: HF and HD LAN-ATG regimens are effective in normalizing IGF-I values in about one-third of patients with active acromegaly inadequately controlled by long-term conventional SRLs therapy. (J Clin Endocrinol Metab 102: 2454–2464, 2017)
Acromegaly is a chronic disfiguring disease characterized by growth hormone (GH) and consequently insulin-like growth factor-I (IGF-I) hypersecretion causing also development of cardiovascular, respiratory, metabolic, skeletal, and neoplastic complications with significant impact on the patient’s quality of life and survival (1, 2). Treatment of acromegaly aims at normalizing GH and IGF-I hypersecretion, controlling tumor growth, improving symptoms and comorbidities, and decreasing mortality (3).

First-generation somatostatin receptor ligands (SRLs), including octreotide long-acting release (LAR) and lanreotide (LAN) Autogel (LAN-ATG), are the first-line medical therapy of acromegaly (4, 5). Although in clinical trials these drugs were reported to normalize GH and IGF-I in half to two-thirds of the patients (6), the real-life effectiveness resulted to be lower with biochemical control of acromegaly occurring in <50% of patients treated with SRLs (7, 8). Indeed, several patients not achieving biochemical targets during treatment with first-generation SRLs are not fully resistant to these drugs, because a clinically significant decrease (i.e., ≥50%) in serum GH and/or IGF-I is observed in several of these cases (8–10). The current guidelines recommend optimization of SRL dose in patients partially responsive to conventional regimens before switching to other therapeutic options (5).

Such a recommendation is based on the results of studies demonstrating that titration of SRL doses above the conventional regimens may improve the biochemical control of acromegaly (10, 11). However, most of published data on the efficacy and safety of high-dose (HD) SRLs concerned octreotide LAR, whereas it is still uncertain whether similar results may be obtained with LAN-ATG (12). In fact, these two SRLs have different pharmacokinetic profiles (13), which may lead to variable responses after increasing dose or shortening frequency of drug administration.

The objective of this trial was to evaluate the safety and biochemical efficacy of high-frequency (HF; 120 mg/21 days) vs HD (180 mg/28 days) LAN-ATG therapy (maximal dose in conventional regimen, 120 mg/28 days) in patients with persistently uncontrolled acromegaly despite >6 months of conventional SRL therapy.

Methods

Design overview

This was a prospective, multicenter, randomized, and open-label study. Patients were enrolled from 16 September 2013 to 7 July 2015. The protocol was approved by the Ethical Committee of Spedali Civili of Brescia on behalf of the Health Authority (principal investigator A.G. was affiliated during the study period at the University and Spedali Civili di Brescia) and by all local ethical committees of each participating center. All patients gave their written informed consent to participate in the study.

Setting and participants

The trial was conducted in 11 endocrinology clinics in Italy. Patients screened for inclusion were ≥18 years old with biochemically active acromegaly (14), at the time receiving intramuscular injections of octreotide LAR (30 mg/28 days) or subcutaneously injections of LAN-ATG (120 mg/28 days) for >6 months. Patients had baseline random GH levels of ≥1 µg/L and/or IGF-I levels of >1.2 the upper limit of normal (ULN) for age. Patients with discordant GH and IGF-I values (i.e., GH levels of <1 µg/L and IGF-I levels of >1.2 ULN or GH levels of ≥1 µg/L and IGF-I levels of ≤1.2 ULN) under conventional SRL regimen were included in the trial. A GH and IGF-I reduction of ≥50% with SRL therapy at screening compared with pre-treatment values was also required to demonstrate SRL sensitivity. Exclusion criteria were: (1) symptomatic cholelithiasis; (2) heart diseases (i.e., unstable angina, sustained ventricular tachycardia, ventricular fibrillation, or a history of acute myocardial infarction within the 3 months preceding study entry); (3) liver disease (i.e., cirrhosis, chronic active hepatitis or chronic persistent hepatitis, or persistent alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase 2-fold the ULN, total bilirubin 1.5-fold the ULN); (4) creatinine 1.5-fold the ULN; (5) radiotherapy for acromegaly in the 5 years before the enrolment; (6) surgery for acromegaly in the 6 months before the enrolment; (7) treatment with pegvisomant or dopamine agonists; (8) previously demonstrated intolerance to LAN; (9) pregnancy or lactation.

Randomization and interventions

The study duration was 28 weeks: 4-week screening period (i.e., patients were treated with octreotide LAR or LAN-ATG at conventional doses) and 24-week randomized treatment period (i.e., patients with treated with LAN-ATG at HF or HD). Screening of patients was performed before the administration of the last conventional dose of octreotide LAR (30 mg every 28 weeks) or LAN-ATG (120 mg every 28 weeks). Four weeks later, eligible patients were randomized to LAN-ATG at 120 mg administered every 21 days for 24 weeks (HF group) or LAN-ATG at 180 mg administered every 28 days for 24 weeks (HD group) (Supplemental Fig. 1). LAN-ATG at 180 mg was administered as two 90-mg injections. Patients were allocated to one of two treatment arms in a 1:1 ratio by a six-patient block randomization. The system was reviewed by a biostatistics quality assurance group and locked after approval.

Outcomes and follow-up

The primary outcome measures were normalization of serum IGF-I (i.e., values ≤1.2 ULN) and decrease of random GH < 1 µg/L at the end of follow-up (i.e., 24 weeks of treatment). The secondary outcome measures were mean change in IGF-I and GH serum concentrations from baseline to week 12 and 24, the proportions of patients achieving IGF-I and GH reduction ≥20% (to limit confounding effect of assay variability), differences in biochemical response of acromegaly and serum LAN values between the two therapeutic arms, clinically relevant tumor shrinkage (decrease in maximum diameter of tumor of ≥20% vs baseline) (15, 16), and safety and tolerability evaluations. Patients underwent evaluations at five time points during the study (Supplemental Fig. 1): (1) The screening visit consisted of a clinical and biochemical evaluation of acromegaly and comorbidities to test the inclusion and exclusion criteria of the study. Screening of patients was performed before the
administration of the last conventional dose of octreotide LAR (30 mg every 28 weeks) or LAN-ATG (120 mg every 28 weeks). The acromegaly activity was assessed by centralized measure of random and fasting serum GH and IGF-I concentrations. In 15 patients already treated with LAN-ATG, a blood sample was collected for measurement of baseline LAN values. (2) The second evaluation was performed 4 weeks after screening (before the first administration of the study drugs) only in patients who were deemed eligible for the study after the screening evaluation. At this time, patients underwent a complete clinical, biochemical, and instrumental evaluation consisting in general biochemistry, glucose homeostasis, gallbladder ultrasound, pituitary magnetic resonance imaging (MRI), and electrocardiography. Glucose homeostasis was assessed by the measurement of serum glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and fasting plasma insulin (FPI). Patients were characterized as having diabetes mellitus when FPG levels were ≥126 mg/dL or when they were on active antidiabetic treatments. Impaired fasting glucose (IFG) was defined when FPG fell between 100 and 125 mg/dL. Patients were defined normoglycemic when FPG was <100 mg/dL and HbA1c values were <6%. MRI was performed according to a standardized procedure, and the evaluation of images was centralized and performed by a neuroradiologist blinded to treatment (E.G.). The adenoma size was evaluated and reported as maximum diameter. After these evaluations, the patients were randomized to the two therapeutic arms. (3) The third evaluation was performed 6 weeks after starting study therapy. At this time point only safety endpoints were evaluated using a questionnaire and measuring general biochemistry and glucose homeostasis parameters. Glucose metabolism was defined as worsened during HF or HD LAN-ATG therapy when a progression from normoglycemia to IFG or from IFG to diabetes occurred or when an increase of HbA1c by at least 0.5% was demonstrated. Glucose metabolism was defined as improved when patients with IFG or diabetes showed normalization of FPG and a decrease in serum HbA1c of at least 0.5%. (4) The fourth evaluation was performed 12 weeks after starting study therapy. At this time point, acromegaly activity and serum LAN values were evaluated along with clinical and biochemical measures as evaluated at the third visit. (5) The final visit occurred after 24 weeks of treatment and at this time point patients repeated all the evaluations performed at the screening and randomization. MRI was repeated in 24 out of 30 patients. Mean values of serum LAN at 12 and 24 weeks were used for the correlation analyses with biochemical parameters of acromegaly. Measurement of IGF-I and GH serum concentrations was centralized (G.B., Azienda Socio Sanitaria Territoriale Spedali Civili di Brescia, Brescia, Italy) and performed using an automated immunoassay (Immulite 2000, Siemens Healthcare Diagnostics Products, Llanberis, United Kingdom). The interassay coefficients of variation were 5.7% for GH and 6.2% for IGF-I, whereas the intra-assay coefficients of variation were 3.7% for GH and 3.1% for IGF-I. The sensitivity was 0.01 μg/L for GH and 20 ng/mL for IGF-I. Other biochemical parameters were measured locally using standard commercial assays. IGF-I values were presented as either absolute values or times above ULN. The age-adjusted normal ranges for IGF-I were: 116 to 358 ng/mL, 117 to 329 ng/mL, 115 to 307 ng/mL, 109 to 284 ng/mL, 101 to 267 ng/mL, 94 to 252 ng/mL, 87 to 238 ng/mL, 81 to 225 ng/mL, 75 to 212 ng/mL, 69 to 200 ng/mL, 64 to 188 ng/mL, 59 to 177 ng/mL, and 55 to 166 ng/mL for the ages 21 to 25, 26 to 30, 31 to 35, 36 to 40, 41 to 45, 46 to 50, 51 to 55, 56 to 60, 61 to 65, 66 to 70, 71 to 75, 76 to 80, and 81 to 85 years, respectively. Measurement of serum LAN was performed at baseline and at 12 and 24 weeks of treatment, just before the LAN-ATG injections. The LAN measurement was centralized and performed by radioimmunoassay (Kymos Pharma Services, Barcelona, Spain). Coefficients of variation ranged from 6.48% to 12.26% and sensitivity was 0.08 ng/mL.

**Statistical analysis**

The safety population included all patients who received one or more doses of study medication. The intent-to-treat (ITT) population included all enrolled patients who received one or more doses of study medication and one or more after baseline GH and IGF-I evaluations. Data are presented as median and interquartile range (IQR) unless otherwise stated. A χ² test (or Fisher’s exact test when necessary) and Mann–Whitney non-parametric test were used to compare categorical and quantitative data at baseline. Wilcoxon signed-rank and Friedman tests were used to evaluate change serum IGF-I, GH, and LAN concentrations between baseline and 12 weeks and/or 24 weeks of treatment. Prevalence of patients normalized for IGF-I or GH concentration and 95% confidence interval (CI) was calculated, and a McNemar test was used to evaluate changes from baseline. A univariate logistic regression was implemented to evaluate relationships between covariates and normalization of serum IGF-I during treatment. An odds ratio (OR) and relative 95% CI were calculated. Correlations were sought by calculating a Pearson coefficient. To obtain the optimal threshold of serum LAN values in predicting IGF-I normalization, receiver operating characteristic (ROC) analysis was performed. The sensitivity (the true positive results) and the specificity (the true negative results) of LAN and IGF-I assays were calculated from patients with IGF-I values below and above 1.2 ULN, respectively. Stata 14.1 was used for all analyses, and a P value of <0.05 was considered statistically significant.

**Results**

In total, 32 patients with biochemically active acromegaly were screened in the 11 participating centers. Two patients did not meet the inclusion criteria and were not included in the study. Therefore, 30 patients were enrolled in the study and represented the safety population. The ITT analysis was performed on 29 patients (14 randomized to the HF group and 15 randomized to the HD group), because one patient (in the HF group) received only one drug dose and voluntary dropped out of treatment due to a side effect (see later). Another patient allocated to the HD group and included in the ITT analysis dropped out after 12 weeks of treatment due to persistently high serum IGF-I during the study period. Patient disposition throughout the study is shown in Supplemental Fig. 2. Patients (15 males and 14 females) had a mean (standard deviation) age of 52 (13.7) years. Out of these 29 patients, 17 had previously undergone neurosurgery, whereas gamma knife and conventional radiation therapy had been performed in two and one patients, respectively, >5 years before the enrolment. Table 1 shows...
the clinical and demographic characteristics at baseline of the 30 patients randomized to the two therapeutic schemes. Patients randomized to HD LAN-ATG had significantly higher serum IGF-I values as compared with patients randomized to HF LAN-ATG (Table 1).

At screening, 26 patients had both GH levels $\geq 1 \, \mu g/L$ and IGF-I levels $> 1.2$ ULN for age and sex, whereas biochemical data were discordant in the remaining three patients (two patients with “safe” GH but high IGF-I, one patient with high GH and normal IGF-I).

### Efficacy

#### Serum IGF1 concentrations

In the whole ITT population (29 patients), serum IGF-I decreased significantly during the study period [from median of 430.0 ng/mL (IQR, 334 to 484) to 382 ng/mL (IQR, 282 to 458); $P = 0.007$]. Analyzing data separately for the two therapeutic arms, a significant decrease in serum IGF-I values was observed in the HD group ($P = 0.006$, 12 weeks vs baseline; $P = 0.03$, 24 weeks vs baseline) but not in the HF group ($P = 0.38$, 12 weeks vs baseline; $P = 0.08$, 24 weeks vs baseline) (Fig. 1). Serum IGF-I normalized in 27.6% of the patients ($P = 0.016$ vs baseline), and at the follow-up the rate of IGF-I normalization was not significantly different between the HD and HF groups (26.7% vs 35.7%; $P = 0.59$) (Supplemental Fig. 3). In the HD group, the number of patients showing a $\geq 20\%$ reduction in serum IGF-I concentrations was higher as compared with the HF group (53.3% vs 21.4%; $P = 0.05$). In the whole ITT population, IGF-I values at the end of follow-up were significantly correlated with baseline IGF-I values ($r = 0.77; P < 0.001$; Fig. 2). Moreover, normalization of IGF-I was significantly predicted by baseline IGF-I (OR, 0.987; 95% CI, 0.976 to 0.998; $P = 0.02$). In the HF therapeutic arm, patients who normalized serum IGF-I had baseline serum IGF-I significantly lower than those who did not achieve IGF-I normalization ($P = 0.01$). Such a difference was not significant ($P = 0.26$) in patients treated with HD LAN-ATG. Indeed, all patients who normalized serum IGF-I during HF LAN-ATG treatment had baseline serum IGF-I $> 1.5$ ULN (Fig. 2). Normalization of serum IGF-I was not significantly predicted by previous treatment with octreotide LAR (OR, 1.25; 95% CI, 0.26 to 6.07; $P = 0.78$).

#### Serum GH concentrations

In the ITT population, serum GH values did not change significantly during the study period [from median 2.3 $\mu g/L$ (IQR, 1.5 to 3.7) to 2.0 $\mu g/L$ (IQR, 1.3 to 3.6); $P = 0.22$]. The percentages of patients experiencing $\geq 20\%$ decrease in serum GH values were not significantly different between the HD and HF groups (35.0% vs 40.0%; $P = 0.65$). By week 24, four patients showed GH values $< 1 \, \mu g/L$ (Supplemental Fig. 3), with comparable rates between HF and

---

### Table 1. Clinical and Biochemical Characteristics at Baseline of 30 Patients Enrolled in the Study and Randomized to Two Therapeutic Arms (HF and HD LAN-ATG)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HF LAN-ATG</th>
<th>HD LAN-ATG</th>
<th>$P$ Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>9/6</td>
<td>6/9</td>
<td>0.273</td>
</tr>
<tr>
<td>Age, y</td>
<td>51.2 (35.5–58.1)</td>
<td>54.6 (45.7–67.1)</td>
<td>0.120</td>
</tr>
<tr>
<td>Previous surgery, n (%)</td>
<td>9 (60.0%)</td>
<td>8 (53.3%)</td>
<td>0.713</td>
</tr>
<tr>
<td>Previous medical therapies</td>
<td></td>
<td></td>
<td>0.710</td>
</tr>
<tr>
<td>LAN-ATG, n (%)</td>
<td>7 (46.7%)</td>
<td>8 (53.3%)</td>
<td></td>
</tr>
<tr>
<td>Octreotide LAR, n (%)</td>
<td>8 (53.3%)</td>
<td>7 (46.7%)</td>
<td></td>
</tr>
<tr>
<td>Previous radiotherapy, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14 (93.3%)</td>
<td>13 (86.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Conventional</td>
<td>0</td>
<td>1 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Gamma knife</td>
<td>1 (6.7%)</td>
<td>1 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Serum GH values, $\mu g/L$</td>
<td>2.4 (1.7–3.9)</td>
<td>2.3 (1.5–3.5)</td>
<td>0.604</td>
</tr>
<tr>
<td>Serum IGF-I values, ULN</td>
<td>1.49 (0.77–2.22)</td>
<td>1.90 (1.18–2.62)</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>132.5 (110–140)</td>
<td>126.5 (120–136)</td>
<td>0.945</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80 (70–90)</td>
<td>80 (70–90)</td>
<td>0.708</td>
</tr>
<tr>
<td>Serum HbA1c values, %</td>
<td>5.9 (5.5–6.2)</td>
<td>6.0 (5.7–6.5)</td>
<td>0.335</td>
</tr>
<tr>
<td>FPI, pg/mL</td>
<td>8.6 (6.8–11.7)</td>
<td>7.5 (5.2–10.6)</td>
<td>0.547</td>
</tr>
<tr>
<td>FPG, mg/dL</td>
<td>99 (94–107)</td>
<td>102 (99–117)</td>
<td>0.151</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>7 (46.7%)</td>
<td>9 (60.0%)</td>
<td>0.715</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>3 (20.0%)</td>
<td>4 (26.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>IFG, n (%)</td>
<td>4 (26.6%)</td>
<td>9 (60.0%)</td>
<td>0.139</td>
</tr>
<tr>
<td>Sleep apnea syndrome</td>
<td>4 (26.6%)</td>
<td>8 (53.3%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Arthopathy</td>
<td>3 (20.0%)</td>
<td>7 (46.7%)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Data are presented as median and IQRs, and the comparisons were performed by nonparametric tests.
HD arms (14.2% vs 13.3%; *P* = 1.0). A full biochemical control of acromegaly (GH < 1 μg/L and IGF-I < 1.2 ULN) was achieved in three patients (one in the HF group and two in the HD group; 10.3%; 95% CI, 2.2% to 27.4%; *P* = 0.50 vs baseline).

**Other efficacy analysis**

In 15 patients in whom sequential serum LAN measurements were performed, a significant increase in serum drug values was observed during 24 weeks of treatment (from median 4.4 ng/mL [IQR, 3.6 to 5.4] to 8.6 ng/mL [IQR, 6.4 to 9.3]; *P* = 0.002) (Fig. 3). In the whole ITT population, serum LAN at 12 to 24 weeks of treatment (i.e., mean of the two time point values in each patient) tended to be lower in the HF group as compared with the HD group [5.4 ng/mL (IQR, 5.2 to 7.4) vs 8.6 ng/mL (IQR, 5.8 to 9.2); *P* = 0.07]. Serum LAN values at these time points were significantly correlated with percentage variations in serum IGF-I (*r* = −0.39; *P* = 0.04) (Fig. 4), but not with normalization of serum IGF-I (OR, 1.31; 95% CI, 0.95 to 1.81; *P* = 0.10) and GH (OR, 0.88; 95% CI, 0.6 to 1.3; *P* = 0.54). The ROC analysis, performed with pooled serum LAN concentrations at 12 and 24 weeks of treatment, showed that 6.8 ng/mL was the best serum LAN cutoff to identify patients with IGF-I values <1.2 ULN at the end of follow-up (sensitivity, 66.7%; specificity, 65%) (Fig. 5). Tumor size did not change significantly in the 24 patients in whom MRI was repeated at the end of follow-up.

**Safety and tolerability**

Overall, 19 patients (63.3%) experienced one or more adverse events that were not reported at study entry. A total of 65 side effects were reported, only one of which was considered serious, although not drug-related. Specifically, one patient, who had been already treated with octreotide LAR, experienced thoracic pain 48 hours after the first 120-mg dose of LAN-ATG in the HF group. The patient was hospitalized and all of the examinations excluded that the aforementioned symptoms were caused by ischemic heart disease. The patient refused to continue treatment. Drug-related gastrointestinal adverse events were reported in 14 out of 30 patients (46.6%); all were mild to moderate and transient in nature and included diarrhea (n = 13), flatulence (n = 2), and abdominal pain (n = 7). Additionally, one patient allocated to the HD therapeutic arm experienced asymptomatic colelithiasis deemed to be related to the study drug. The incidence of gastrointestinal adverse effects was not significantly different between study groups. In the whole population, no significant changes vs baseline were observed in FPI, FPG, and HbA1c (Supplemental Table 1). Four patients (13.3%; three in the HD group and one in the HF group) with preexisting IFG showed an improvement of glucose
homeostasis with normalization of FPG at the end of follow-up ($P = 0.125$ vs baseline). Four other patients (13.3%; all in the HF group) with pre-existing normal FPG developed IFG during the study period ($P = 0.125$ vs baseline). Three patients (10%; all in the HD group) with pre-existing IFG developed diabetes during the study period ($P = 0.25$ vs baseline). All patients newly developing either diabetes or IFG maintained active acromegaly during LAN-ATG treatment. No electrocardiography abnormalities were registered during the study period.

**Discussion**

This randomized study shows that increasing the dose and frequency of LAN-ATG normalized serum IGF-I in about a third of acromegaly patients inadequately controlled during conventional SRL therapeutic regimens. Indeed, the decrease in serum IGF-I values was greater in patients treated with HD LAN-ATG as compared with those on HF LAN-ATG. Interestingly, we also found a significant correlation between a decrease in serum IGF-I and an increase in serum LAN values during increasing dose or frequency of LAN-ATG.

Partial responsiveness to SRLs is a frequent condition in real-life circumstances, involving up to 50% of patients not achieving biochemical targets during treatment with SRLs at conventional doses (10). Indeed, partial responsiveness to SRLs is a gray area in which patients with various degrees of clinical responsiveness may fall. Some patients may improve their clinical symptoms and comorbidities regardless of strict biochemical control of acromegaly (17, 18), whereas others may show persistency or progression of comorbidities (19, 20) even when the biochemical targets are achieved. However, the definition of partial responsiveness to SRLs is currently based on biochemical criteria, and the guidelines (5) as well as the real-life evidence (7) suggest therapeutic adjustment based on absolute GH and IGF-I levels (5). In fact, achievement of safe GH and normal IGF-I are needed to normalize mortality rate in acromegaly (21).

Pharmacokinetic and pharmacodynamic studies have established that current SRL regimens do not ensure the maximum biochemical effect in acromegaly patients, likely due to variability in circulating drug values (22), incomplete saturation of somatostatin receptors on the tumor (23), and lack of binding to somatostatin receptors, such as the subtype 5, for which these drugs have low affinity (24). Based on these concepts, the increase of SRL dose over the conventional regimens has been proposed as a possible strategy to achieve the biochemical targets in acromegaly patients with demonstrated partial response to conventional regimens (12). Former studies demonstrated that increasing the octreotide LAR dose to 40 or 60 mg every 24 weeks was effective in normalizing serum IGF-I in a subset of patients who had not been controlled by the maximum conventional SRL doses (10, 11). Of note, the therapeutic improvement was not achieved by shortening the frequency of octreotide LAR administration (11). Data on high doses of LAN-ATG are still anecdotal, based on small series of patients or single cases enrolled in trials in whom titration of drug doses was occasionally performed to try achieving biochemical control of acromegaly (25–27).
This randomized study investigated the efficacy and safety of HD and HF LAN-ATG in partial responder acromegaly patients. Consistent with the former trial performed with octreotide LAR (11), this study showed that HD of LAN-ATG led to a greater decrease in serum IGF-I values as compared with HF LAN-ATG. Overall, more than one-third of the study patients had normal IGF-I levels at the end of the study with a similar rate of normalization in the HD and HF arms. Baseline IGF-I levels strongly predicted IGF-I normalization specifically during HF LAN-ATG treatment. In fact, normalization in serum IGF-I was observed in patients treated with HF LAN-ATG only when their baseline IGF-I was <1.5 ULN, whereas in HD LAN-ATG patients normalization of IGF-I occurred also with higher baseline values. One could argue that pursuing normalization of hormonal values by increasing dose or frequency of LAN-ATG may not be cost-effective in patients with a mild increase of IGF-I level. Indeed, strict biochemical control of acromegaly was shown to reduce the economic burden of acromegaly regardless of the drug cost, which appeared to have a relevant impact only in patients with uncontrolled disease (28, 29). Moreover, a linear correlation between serum IGF-I values and metabolic abnormalities was reported (30), and a minimal decrease in serum IGF-I values was associated with significant improvement of survival in acromegaly (21, 31). In fact, in real-life circumstances, slightly reduced serum IGF-I values (i.e., 1.4 vs 1.2 ULN) were found to be associated with decreased mortality in acromegaly patients (32). Besides these considerations, it is noteworthy that the results of this trial were partially different from those performed with octreotide LAR (11). In fact, in the former trial no clear-cut relationship of IGF-I normalization with baseline IGF-I levels was observed. Moreover, octreotide LAR was not shown to be effective in the HF regimen in normalizing serum IGF-I even in patients with lower baseline hormonal values (11). The discordant results between octreotide LAR and LAN-ATG when administered at HF may reflect different pharmacokinetic profiles of the two drugs characterized by a quite rapid decrease in serum LAN after the drug administration as compared with octreotide LAR, which instead maintains high serum values for 3 to 4 weeks (13). Interestingly, our study population was quite similar to that enrolled in the PAOLA (pasireotide versus with octreotide or lanreotide in inadequately controlled acromegaly) study, in which there were enrolled patients inadequately controlled by SRLs without preselection based on the degree of SRL sensitivity, and the rate of IGF-I normalization that we observed was comparable to that reported with pasireotide LAR in that former study (33). This observation may be explained by the spillover effect of LAN at high concentrations on subtype 5 of the somatostatin receptor (34). Alternatively, it may be hypothesized that also for pasireotide LAR, such as for first-generation SRLs, higher doses than those currently used could be more effective in normalizing IGF-I.

Another peculiarity of this study was the evaluation of serum LAN values in all patients undergoing treatment with HF or HD LAN-ATG. Interestingly, we found a significant correlation between serum LAN values measured after 12 to 24 weeks of treatment and entity of IGF-I decrease induced by HF or HD LAN-ATG.
This finding, along with the increase in serum LAN concentrations during the follow-up in the subset of patients in whom sequential measurements were performed, is consistent with the working hypothesis that improvement in biochemical control of acromegaly by increasing LAN-ATG dose or frequency was a direct consequence of enhanced drug availability achieved after titration of therapy over the conventional regimens (22, 23). In fact, the cutoff serum LAN value able to predict IGF-I normalization identified by ROC analysis was higher than values already observed in patients treated with LAN-ATG at conventional doses (35, 36) as well as in our patients with active acromegaly before starting HD and HF regimens. Therefore, assessment of circulating LAN values could be suggested to be helpful in monitoring drug titration in acromegaly patients resistant to conventional regimens of LAN-ATG. However, normalization of IGF-I was more correlated with baseline hormonal values than LAN concentrations achieved during treatment. One could argue that HD of LAN-ATG adopted in this study were relatively lower than those already used in the HD octreotide LAR trial (i.e., 1.5-fold vs 2.0-fold the maximal conventional doses) (11).

Consistent with the pathophysiological concept that at high SRL concentration in the blood a spillover effect on other somatostatin subtype receptors (particularly the subtype 5) may occur (34), it could be hypothesized that a further increase in LAN-ATG dose (i.e., up to 240 mg every 28 days) may produce even better disease control, making the biochemical response possibly less dependent on baseline IGF-I levels.

This study did not demonstrate a significant shrinkage of tumor mass after increasing dose or frequency of LAN-ATG. Indeed, the lack of evident shrinkage in our patients may have been influenced by the fact that most of enrolled patients had been treated by neurosurgery. In fact, evaluation of tumor shrinkage in patients who have previously undergone surgery or radiotherapy is quite difficult since transphenoidal resection induces anatomical sellar alterations that result in poor reproducibility when evaluating pituitary imaging (15, 16). Moreover, most of our patients had a long duration of SRL therapy, and previous studies demonstrated that tumor shrinkage tends to occur mainly during the first 6 to 12 months of treatment (37, 38).

With regard to the safety of the HD or HF regimens, we did not observe relevant changes in liver and other routine biochemical parameters. Of note, HF and HD LAN-ATG did not induce relevant changes in glucose metabolism, as assessed by measurement of FPG and serum HbA1c. Interestingly, about one-third of patients with baseline IFG normalized FPG after increasing dose or frequency of LAN-ATG, likely reflecting an improvement in biochemical control of acromegaly. These results were consistent with those obtained with octreotide LAR at conventional doses as well as at higher doses (39, 40), but they did not reflect the hyperglycemic risk observed with pasireotide LAR in the PAOLA (pasireotide versus with octreotide or lanreotide in inadequately controlled acromegaly) study (33, 41, 42).

Some limitations of this study are worth mentioning. In acromegaly, control of comorbidities have a definitive impact on quality of life and mortality (31, 32), and the benefits of biochemical control of acromegaly on the outcome of comorbidities in each patient are not completely predictable (29). This multicenter study was not designed to provide a comprehensive and objective

Figure 4. Correlation between percentage change in serum IGF-I and serum LAN values, as measured by pooling the samples at 12 and 24 weeks of treatment with HF (120 mg every 3 weeks; ○) and HD (180 mg every 4 weeks; ■) LAN-ATG.

Consistent with the pathophysiological concept that at high SRL concentration in the blood a spillover effect on other somatostatin subtype receptors (particularly the subtype 5) may occur (34), it could be hypothesized that a further increase in LAN-ATG dose (i.e., up to 240 mg every 28 days) may produce even better disease control, making the biochemical response possibly less dependent on baseline IGF-I levels.

This study did not demonstrate a significant shrinkage of tumor mass after increasing dose or frequency of LAN-ATG. Indeed, the lack of evident shrinkage in our patients may have been influenced by the fact that most of enrolled patients had been treated by neurosurgery. In fact, evaluation of tumor shrinkage in patients who have previously undergone surgery or radiotherapy is quite difficult since transphenoidal resection induces anatomical sellar alterations that result in poor reproducibility when evaluating pituitary imaging (15, 16). Moreover, most of our patients had a long duration of SRL therapy, and previous studies demonstrated that tumor shrinkage tends to occur mainly during the first 6 to 12 months of treatment (37, 38).

With regard to the safety of the HD or HF regimens, we did not observe relevant changes in liver and other routine biochemical parameters. Of note, HF and HD LAN-ATG did not induce relevant changes in glucose metabolism, as assessed by measurement of FPG and serum HbA1c. Interestingly, about one-third of patients with baseline IFG normalized FPG after increasing dose or frequency of LAN-ATG, likely reflecting an improvement in biochemical control of acromegaly. These results were consistent with those obtained with octreotide LAR at conventional doses as well as at higher doses (39, 40), but they did not reflect the hyperglycemic risk observed with pasireotide LAR in the PAOLA (pasireotide versus with octreotide or lanreotide in inadequately controlled acromegaly) study (33, 41, 42).

Some limitations of this study are worth mentioning. In acromegaly, control of comorbidities have a definitive impact on quality of life and mortality (31, 32), and the benefits of biochemical control of acromegaly on the outcome of comorbidities in each patient are not completely predictable (29). This multicenter study was not designed to provide a comprehensive and objective

Figure 4. Correlation between percentage change in serum IGF-I and serum LAN values, as measured by pooling the samples at 12 and 24 weeks of treatment with HF (120 mg every 3 weeks; ○) and HD (180 mg every 4 weeks; ■) LAN-ATG.
evaluation of symptoms and signs of acromegaly before and after HD and HF LAN-ATG therapy (2), and the follow-up was likely too short to allow a reliable estimate of comorbidities outcome during treatment. Moreover, the study was thought to be likely underpowered to evaluate clinical endpoints. The short period of the study likely led to an underestimate of the therapeutic effects of HD and HF LAN-ATG because previous studies demonstrated a close relationship between duration of treatment and biochemical control of acromegaly (6, 43). However, the 24-week study period was selected as the shortest period in which sustained biochemical and clinical effects of treatment could have occurred (11, 24), avoiding potential ethical issues related to prolongation of hitherto unproven study treatment beyond this period. The small size of study groups, related to the rarity of disease, is a limitation of the study. However, the number of patients enrolled was sufficient to demonstrate, with a rigorous study design, that increasing dose or frequency of LAN-ATG can normalize serum IGF-I. As already reported in several trials (6, 44, 45) and also observed for octreotide LAR at HD (11), LAN-ATG at HD or HF was shown to be largely more effective on serum IGF-I as compared with serum GH values. This result may be due to the stringent criteria used in this trial to define safe GH values, as compared with other studies (11, 33). Alternatively, it could be hypothesized that using HD or HF LAN-ATG may amplify the direct inhibition of peripheral synthesis of IGF-I by LAN-ATG (46, 47). Nevertheless, it is plausible that random GH may have provided less information on biochemical and clinical outcome acromegaly as compared with IGF-I (30, 48, 49). Histopathologic and molecular characteristics of GH-secreting pituitary adenomas have been proposed as biomarkers of responsiveness to SRLs (50, 51). However, histopathological data were not collected in this study because only 17 out of 30 of our patients had undergone pituitary surgery; moreover, the multicenter nature of the study was thought to cause a lack of homogeneity in the histopathologic reports from patients operated on in different time periods.

Besides the aforementioned limitations, our trial provides convincing evidence that LAN-ATG is safe and effective when used at high doses and frequencies, reinforcing the concept supported by the current guidelines that drug titration over the conventional regimen should be undertaken in acromegaly patients partial responders to conventional SRL doses before switching to other treatment options.

Acknowledgments

We thank the following colleagues for their contributions to conducting the trials: M. Albizzi (Bergamo, Italy), M. Ferrata (Padua, Italy), A. Frigo (Verona, Italy), I. Karamouzis (Turin, Italy), F. Grimaldi (Udine, Italy), G. Marcelli (Ancona, Italy), E. Nazzari (Genoa, Italy), T. Porcelli (Brescia, Italy), M. Ragonese (Messina, Italy), G. Reimondo (Turin, Italy), I. Tenuti (Verona, Italy), M.L. Torre (Messina, Italy), and B. Zampetti (Milan, Italy). We also thank Dr. V. Panetta for the statistical support in the analyses of data.

A. Giustina’s current affiliation is Chair of Endocrinology, San Raffaele Vita-Salute University, 20132 Milan, Italy.

Address all correspondence and requests for reprints to: Andrea Giustina, MD, San Raffaele Vita-Salute University, Via Olgettina 60, 20132 Milan, Italy. E-mail: a.giustina@libero.it.

This study was sponsored by Azienda Socio Sanitaria Territoriale Spedali Civili di Brescia (with unrestricted financial support from Ipsen) and Glucocorticoid Induced Osteoporosis Skeletal
References


