CLINICAL STUDY

Slow-release lanreotide in the treatment of acromegaly: a study in 66 patients

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Abstract

Objective: Slow-release (SR) lanreotide is a long-acting somatostatin analog that has been developed in order to overcome the inconvenience of multiple daily subcutaneous injections of octreotide, required for metabolic control in acromegaly. Lanreotide SR has been found to be well tolerated and effective in reducing GH and IGF-I levels but clinical data are still limited compared with those with subcutaneous octreotide treatment.

Design: Sixty-six unselected patients with active acromegaly were therefore evaluated in a multi-center, prospective, open label study. Lanreotide SR was given at a dose of 30 mg intramuscular every 7±14 days.

Methods: At baseline and after 2, 4, 8, 12, 24, 36 and 48 weeks patients underwent a clinical examination with assessment of acromegaly related symptoms, and blood was sampled for serum GH, IGF-I, prolactin, glycosylated hemoglobin, fasting glucose, hematology, kidney function and liver function tests. Biliary ultrasonography and pituitary magnetic resonance imaging were performed at baseline and after one year.

Results: Treatment resulted in a significant improvement in the symptom score from 2.69 ± 0.27 to 1.06 ± 0.17 (P < 0.0001). Serum IGF-I levels fell from 699 ± 38 µg/l at baseline to 399 ± 26 µg/l (P < 0.0001, n = 60) after one month, after which levels remained stable: 480 ± 37 µg/l after 6 months (n = 54) and 363 ± 32 µg/l after one year (n = 46). GH levels dropped from 13.8 ± 3.2 µg/l to 4.3 ± 0.7 µg/l after one month (P < 0.0001, n = 60) and remained stable thereafter: 3.9 ± 0.4 µg/l (n = 54) after 6 months and 3.5 ± 1.1 µg/l after one year (n = 46). Twenty-nine out of 66 patients (44%) attained a normal age-corrected IGF-I level and 30 patients (45%) attained a GH level below 2.5 µg/l. Pituitary adenoma shrinkage of at least 25% was found in 5 of 14 patients (36%) after one year. Side effects were mainly transient gastrointestinal symptoms and pain at the injection site, resulting in drug discontinuation in only 6 patients (9%). Two patients developed new gall stones. No difference was found between subcutaneous octreotide and lanreotide SR in efficacy and almost all patients preferred the easier dose administration of lanreotide SR.

Conclusions: Long-term treatment of acromegaly with SR-lanreotide is effective in controlling GH and IGF-I levels and symptoms and is well tolerated in the majority of patients. Compared with subcutaneous octreotide, lanreotide SR considerably improves patient’s acceptance of therapy while having the same overall efficacy.

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Introduction

Growth hormone (GH)-secreting pituitary adenomas are the most common cause of the acromegalic syndrome (1). In view of the increased mortality associated with acromegaly, a successful management is of utmost importance, as reduction of the GH concentration below 5 mU/l allows a shift of the mortality rate into the normal range (2). Selective resection of the adenoma by the transsphenoidal approach is the treatment of choice for acromegaly (3). Taking into account the confusion about what should be considered the ‘universal’ standard for GH and insulin-like growth factor-I (IGF-I) determination,
the overall rate of success with surgery is < 50% when a postoperative serum GH level below 2.5 μg/l and/or a normal serum IGF-I level are used (4–6). Therapeutic effects of pituitary radiation are usually not measured against these criteria and, are, moreover, slow to develop (7). These findings clearly indicate the necessity for adequate adjunctive medical treatment.

Much medical experience has been obtained with the dopamine agonist bromocriptine (8) and, more recently, cabergoline (9), indicating that normal IGF-I levels can be obtained in 10–43% of cases. Comparative studies, however, have shown that bromocriptine is less effective in the suppression of GH and IGF-I secretion than somatostatin analogs (10, 11). The latter are able to normalize IGF-I levels in 30–80% of subjects, but the necessity of daily subcutaneous injections is a major drawback of therapy (12, 13). Two new long-acting somatostatin analogs have recently been developed to overcome this limitation. The first is the depot formulation of octreotide, Sandostatin LAR, which works during 28 days after a single intramuscular injection and was found to compare favorably with the subcutaneous form of octreotide (14, 15). The second long-acting somatostatin analog is Lanreotide Slow Release (SR). Lanreotide is a cyclic octapeptide analog, which possesses a prolonged duration of action of between 10 and 14 days, due to the incorporation of the analog in microspheres. Several clinical studies have reported excellent efficacy and tolerance for lanreotide SR (16–26). We examined our own experience in an open labeled multi-center study in a large group of unselected acromegalic patients.

Subjects and methods

Patients

Sixty-six patients with active acromegaly, 37 males and 29 females, aged 49.6 ± 3 years (mean ± s.e.m., range 29–82 years), were enrolled in this prospective, multi-center open labeled study. The Belgian patients were recruited from 8 different centers each including between 2 and 7 patients. The 29 Italian patients originated from one center. Informed consent was obtained from all patients. Diagnosis of acromegaly was established by the inability to suppress GH levels below 2 μg/l after ingestion of 75 g glucose and by the presence of serum IGF-I levels above the normal range. Prior to the study, 34 of 66 patients (52%) had been submitted to neurosurgery. The time interval between the operation and the study was 6.0 ± 0.9 years (range 0.5–19 years). Surgery was followed by radiotherapy in 14 patients. Another 3 patients received radiotherapy as primary therapy, making a total of 17 patients with previous radiotherapy (26%). Radiotherapy was given 4.5 ± 0.7 years (range 1–14 years) before the study. Dopamine agonist therapy, bromocriptine or cabergoline, was given to 35 patients (53%), either as primary therapy (15 patients) or after surgery and/or radiotherapy (20 patients). Four of these patients were considered to have a mixed growth hormone-prolactin (GH-PRL) secreting adenoma. All except one had not been controlled by dopamine agonist therapy alone. Fifty-five of 66 patients (83%) had previously been given subcutaneous octreotide, of whom 14 received it as primary therapy and 41 in adjunction to other forms of therapy. In this group, 19 patients (35%) obtained a normal IGF-I level using a mean octreotide dose of 513 ± 95 μg/day (range 100–1500 μg/day) during 31.7 ± 4.1 months (range 2–123 months). Three patients (4.5%) had no previous treatment. Twenty-two of 66 patients (33%) had a macroadenoma, 10 patients a microadenoma (16%), whereas 34 patients (51%) had a parasellar or intrasellar remnant after surgery.

Study protocol

Lanreotide SR (Ipsen-Beaufour, Signes, France; Somatuline LA in Belgium and Ipystil in Italy) was started at a regimen of one intramuscular injection of 30 mg every two weeks. In this study normalization of serum IGF-I levels was considered to express normalization of GH production and was used as the main parameter for adaptation of the dose, although controversy exists about this view (4, 5). In case of insufficient therapeutic response (defined as an elevated serum IGF-I) after three months of therapy, the interval between two injections was shortened to 10 days, and, if considered necessary after an additional three months, to 7 days. Final results were evaluated after one year of therapy, unless the study was interrupted at an earlier stage. In 4 patients partly responsive to bromocriptine, the dose was continued unaltered throughout the study. A washout period of at least one week was respected in all but 24/66 patients. In these patients baseline values were taken as those pertaining before starting subcutaneous octreotide treatment.

Serum IGF-I and GH concentrations were measured before the start of the treatment, every 2–4 weeks in the dose finding period and every 3 months thereafter, before a new injection was given. Serum IGF-I concentrations were considered normal if they fell between the limits for the age group in every center. Serum GH, the mean of 3–5 samples taken at 30–60 min intervals, was considered safe if the value was less than 2.5 μg/l. For clinical evaluation, the patients were asked to judge symptoms (headache, paresthesiae, arthralgia, hyperhydrosis and carpal tunnel syndrome) on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). They were also asked if they preferred short-acting octreotide or lanreotide as a long-term therapy. Laboratory tests also included fasting blood glucose levels, glycosylated hemoglobin (HbA1c) levels, kidney function and liver function tests. Magnetic resonance imaging of the pituitary region was performed at baseline and after one year. Tumor

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shrinkage was judged by each investigator in every center, using three diameters. Abdominal ultrasound was also performed at baseline and at the end of the first year.

The number of patients available for analysis at each time point were: start n = 66, 14 days n = 48, 1 month n = 61, 3 months n = 57, 6 months n = 54, 9 months n = 52, 12 months n = 46. Twenty patients discontinued therapy before the 1 year analysis due to poor local tolerability (n = 3), gastrointestinal side effects (n = 3), pregnancy (n = 1), preference for surgery (n = 1), change of therapy because of inefficacy (n = 9), noncompliance or lost to follow-up (n = 3).

**Hormone assays**

Serum IGF-I and GH were measured in each center by commercially available kits. IGF-I values were measured after ethanol extraction and a polyclonal assay was used for GH.

**Statistics**

All results are expressed as percentages of the total or as the mean ± S.E.M. and by the range if this was considered useful. Differences between groups were tested by the Student’s t-test with significance set at the P < 0.05 level.

**Results**

**Clinical symptoms**

With therapy, the mean symptom score decreased from 2.69 ± 0.27 to 1.06 ± 0.17 (P < 0.0001). Twelve of 66 patients (18%) had no symptoms at the start of therapy (symptom score 0) and could therefore not improve. At the end of therapy, the number of patients with a symptom score of 0 increased to 33 (50%). Patients without symptoms at the end of the evaluation period had a normal IGF-I in a higher percentage of cases (55%, median IGF-I level 270 μg/l) compared with patients with persistent symptoms (27%, median IGF-I level 375 μg/l, Chi-square test P = 0.045).

In all but three patients (with severe local pain after the intramuscular injection) lanreotide SR was considered much more convenient than octreotide because of the fewer injections needed.

**Biochemical effects of lanreotide SR on GH and IGF-I (Fig. 1)**

With therapy, serum IGF-I levels fell from 699 ± 38 μg/l at baseline to 399 ± 26 μg/l (P < 0.0001, n = 60) after one month, after which levels remained stable: 480 ± 37 μg/l after 6 months (n = 54) and 363 ± 32 μg/l after one year (n = 46). If patients who dropped out of the study are included with their last results, IGF-I levels dropped from 699 ± 38 μg/l (range 349–1980 μg/l, median 640 μg/l) to 381 ± 25 μg/l (range 105–1440 μg/l, median 343 μg/l, P < 0.0001). Twenty-nine out of 66 patients (44%) obtained a normal IGF-I level. In the patients who did not reach this end point, a mean reduction in IGF-I values of 30.4 ± 5.0% (range 0–71%, median 30.5%) compared with baseline was observed.

Similarly, within one month GH levels dropped from 13.8 ± 3.2 μg/l to 4.3 ± 0.7 μg/l (P < 0.0001, n = 60) and remained stable thereafter: 3.9 ± 0.4 μg/l (n = 54) after 6 months and 3.5 ± 1.1 μg/l after one year (n = 46). If patients who dropped out of the study are included with their last results, serum GH levels fell from 13.8 ± 3.2 μg/l (range 1.6–188 μg/l, median 7 μg/l) to 5.0 ± 1.3 μg/l (range 0.7–67.3 μg/l, median 2.7 μg/l, P = 0.00014). GH levels were suppressed to below 2.5 μg/l in 30 patients (45%) and to below 5 μg/l in another 26 patients (40%). Patients not reaching a GH level less than 2.5 μg/l had a mean drop of 46.9 ± 5.0% (range 0–86%, median 52%) from baseline GH values.

**Dose of lanreotide SR**

All patients started on a regimen of one intramuscular (i.m.) injection every 14 days. In 2 of 66 patients (3%)
the dose was reduced to once every 3 weeks because of side effects (one had pain at the injection site and one had diarrhoea). In 1 of these 2 patients IGF-I normalized, while it remained elevated in the other patient. Thirty-four of 66 patients (52%) continued on one i.m. injection every 2 weeks, while an increase in dose up to once every 10 days was needed in 19 patients (29%) and to once every week in 11 patients (16%). The number of patients obtaining a normal IGF-I level was 19 of 34 patients (56%) in those receiving 2 injections per month. By increasing the dose to 3 injections per month, another 6 of 19 patients (32%) reached normal IGF-I levels and with 4 injections per month another 2 of 11 patients (18%) reached normal IGF-I levels. A technical problem with the injection was encountered once.

**Pituitary tumor size**

The effects of lanreotide SR on tumor size were difficult to evaluate because many patients had had previous surgery and/or radiotherapy, resulting in destroyed architecture of the pituitary region, or they had been treated with octreotide in the period before lanreotide SR. In our series, tumor volume could be evaluated in only 14 of 66 patients (21%). In this small group, 5 of 14 patients (36%) were found to have a decrease in tumor volume of at least 25%, whereas the others were judged as stable. In those with a decreased tumor volume the baseline IGF-I level showed a larger decrease (from 887 to 382 µg/l, -57%) than in those with stable tumor volume (885 to 524 µg/l, -41%).

**Tolerance**

Gastrointestinal complaints were seen in 41 patients (62%). Most prominent problems were diarrhoea, loose stools, abdominal cramps and nausea. These usually occurred within the first 24 h after the i.m. injection and lasted on average 1–3 days (range 0.5–8 days). In the majority of cases, the incidence and severity decreased after the following injections. Gastrointestinal discomfort persisted in 13 of 41 patients (20%) and 3 patients (4.5%) finally stopped therapy for this reason.

Pain at the injection site was a complaint in 18 patients (27%). At the end of the evaluation period local pain after the injection was maintained in 12 patients (18%), but this was only severe enough for 3 patients (4.5%) to withdraw after 2–6 months.

Other side effects, considered to be therapy-related, were dizziness and headaches (each 1 patient or 1.5%). Two patients (3%) developed asymptomatic gall stones during therapy while three others already had gall stones or sludge at the start of therapy. Therapy was continued in all these patients.

No significant difference was noticed in weight: 81.3 ± 2.3 kg at baseline and 82.1 ± 2.6 kg after one year. Fourteen patients (21%) had hypertension at the start of therapy. A slight non significant decrease was noted in systolic and diastolic blood pressure: respectively 133 ± 2 mmHg and 85 ± 1 mmHg at baseline versus 131 ± 2 mmHg and 82 ± 1 mmHg after one year of therapy.

Fasting glucose showed an increasing trend: 5.47 ± 0.27 mmol/l at baseline, 5.53 ± 0.31 mmol/l after 3 months, 5.60 ± 0.32 mmol/l after 6 months, 5.77 ± 0.41 mmol/l after 9 months and 5.88 ± 0.34 mmol/l after 1 year, but the difference was not significant.

Similarly, HbA1c tended to rise slightly: 6.3 ± 0.4% at baseline, 6.5 ± 0.3% after 1 month, 6.6 ± 0.5% after 3 months, 6.5 ± 0.4% after 6 months, 6.8 ± 0.5% after 9 months and 6.5 ± 0.4% after 1 year. This rise was, however, not significant.

Nine of 66 patients (14%) were known to have overt diabetes at the start of therapy. Three of these received insulin injections and six were on oral hypoglycemic medication. No significant modification of carbohydrate tolerance was noted in these patients during therapy.

No impairment of hematology and other biochemistry safety tests was observed.

**Subgroup analysis**

**Octreotide-responsive versus octreotide-non responsive**

Fifty-five patients had previously been treated with subcutaneous octreotide. In 14 of the 19 patients (74%) previously normalized with octreotide, a normal IGF-I level was reached with lanreotide SR, while IGF-I levels in the remaining 5 patients were between 330 µg/l and 462 µg/l.

Two patients (4%) were considered intolerant to octreotide. These patients intolerant to octreotide also had gastrointestinal side effects with lanreotide SR (1 temporary, 1 continuing) but could pursue therapy and both achieved a normal IGF-I level.

The remaining 34 (62%) patients had been treated by octreotide at a mean dose of 564 ± 64 µg/day (range 200–1500 µg, median 300 µg/day) without reaching a normal IGF-I value. In this group a normal IGF-I level was obtained in only 5 of 34 patients (15%). The patients responding to lanreotide SR and not to subcutaneous octreotide had been treated with a dose of octreotide between 300 and 900 µg/day and responded now to 2 to 4 injections/month of lanreotide SR.

**Initial GH and IGF-I level**

Patients that reached a GH level below 2.5 µg/l with lanreotide SR tended to have lower baseline GH levels compared with those who did not: 8.2 ± 5.3 µg/l versus 18.0 ± 5.6 µg/l, but the difference was not significant.

Similarly, patients attaining a normal IGF-I level tended to have lower IGF-I levels at baseline than those
who did not: 604 ± 69 versus 758 ± 63 μg/l, although the difference was not significant.

Primary versus secondary therapy In this series, 29 of 66 patients (44%) received somatostatin analogs as primary therapy (either directly or after dopamine agonists). Out of these, 11 reached a normal IGF-I level (42%) compared with 18 of 37 patients (49%) in which somatostatin analogs were used as secondary therapy (no significant difference).

Belgium versus Italy The percentage of patients obtaining a normal IGF-I level or GH levels below 2.5 μg/l with lanreotide SR was equal in Belgium and Italy: 16 of 37 patients (43%) versus 13 of 29 (45%) for IGF-I and 16 of 37 patients (43%) versus 14 of 28 patients (50%) for GH.

Discussion This is one of the largest multi-center trials with lanreotide SR in the treatment of acromegaly published up till now (Table 1). The number of patients included in the present trial allowed us to look for baseline parameters predicting good results and to provide better estimates on tolerance. The limits of the study concern the multi-center character of the trial in which hormones were measured locally in every participating center.

We showed that a normal serum IGF-I was obtained in 44% of patients. This falls within the limits of 23–68% from earlier trials (16–26). The large range in percentage of success can partly be explained by differences in selection of patients. Morange et al. (19), for instance, only included patients who were previously normalized by octreotide, and thus were known beforehand as good responders to somatostatin analogs. We also found a large difference in response between those patients that were previously normalized with octreotide versus those who were not normalized (74 versus 15% normalization of IGF-I). If we compare our results in octreotide-normalized patients to those in the study of Morange et al. (19), the figures are much more similar, with 74% and 68% IGF-I normalization respectively. The evaluation of success rate for GH levels between the different studies is even more difficult as differences in normality vary between 2.5 and 5 μg/l. In addition, many patients with a GH level below 2.5 μg/l during therapy continue to have an elevated IGF-I and vice versa (22).

Apart from octreotide sensitivity, response to treatment was not influenced by sex, previous surgery nor previous radiotherapy, similar to the experience in other studies (25). Patients whose GH or IGF-I levels were not normalized tended to have higher pre-treatment levels, but the difference was not significant. The inter-individual difference in intrinsic sensitivity for somatostatin analogs seems to depend most importantly on number and type of receptors (27).

In our report, a similar number of patients obtained a normal IGF-I level with lanreotide SR as they had done with octreotide previously (both 44%), but 5 patients responded to lanreotide SR although they did not respond to subcutaneous octreotide and vice versa. Although inadequate use of each drug may have allocated patients wrongly in the category of non-responder, a difference in responsiveness to each drug seems a more likely explanation. In agreement with our observation, Colao et al. (24) described recently 4 patients not normalized with octreotide but responding to lanreotide SR. Switching patients from one somatostatin analog to another might therefore occasionally be effective if patients are initially insufficiently controlled. If data from a number of published trials are combined, 220 of 417 acromegalic patients (53%) attained a normal IGF-I with subcutaneous octreotide (28), compared with 134 of 256 patients (52%) with lanreotide SR (if our current results are included together with 9 other trials: 16–24). Although not proven by a randomised double blind clinical trial, these data strongly suggest that both drugs are equally effective. Moreover, both on an anamnetic base (22, our data) and in sequential therapy (24), subcutaneous octreotide and lanreotide SR have been found to be equally effective in the same patients. One study showed that subcutaneous octreotide was able to induce an earlier reduction in IGF-I levels and a more marked reduction in GH levels compared with lanreotide, but after six months of therapy the effect was similar with both drugs (26).

In the present study, we noticed that shortening the drug delivery interval was necessary in 45% of the patients. Shortening the dose interval from 14 to 10 days significantly improved treatment outcome as an additional 6 of 19 patients (32%) obtained a normal IGF-I level with this measure. By contrast, only 2 of 11 patients (18%) reached a normal IGF-I when the interval was further reduced from 10 to 7 days. This can be explained by the specific pharmacological profile of the drug reaching a maximum effect after 9 days: a mean IGF-I suppression of 80% at day 4, 83% at day 9 versus 53% at day 14 was obtained (16). This profile also explains why a further reduction of the dose interval from 10 to 7 days is less beneficial. Similar to our experience, a shortening of the dose interval has been found to be useful in 35–53% of patients in six other studies with lanreotide SR in which dose adaptations were allowed (19–24).

Therapy with lanreotide SR was well tolerated, even at the higher doses. Gastrointestinal side effects initially occurred in 62% of our patients, a number which is close to the 60% with octreotide (29) and falls between the results with other studies (11–100%) employing lanreotide SR (16–26). A relatively high number of patients (27%) complained about pain at the injection site in our analysis and this was severe enough for 3 patients (4.5%) to discontinue therapy. Subcutaneous...
Table 1 Overview of efficacy and tolerability of lanreotide SR in patients with acromegaly.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author (reference)</th>
<th>Number of patients</th>
<th>Frequency of injections</th>
<th>Duration (months)</th>
<th>IGF-I normalization (%)</th>
<th>GH normalization (%)</th>
<th>% GI side effects</th>
<th>% Local side effects</th>
<th>% Drop-outs because of side effects</th>
<th>% Tumor reduction**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Heron et al. (16)</td>
<td>14</td>
<td>all q 14 d</td>
<td>6</td>
<td>13/14 (93%) (&lt; 350 µg/l)</td>
<td>9/14 (64%) (&lt; 5 µg/l)</td>
<td>64</td>
<td>50</td>
<td>NA</td>
<td>15%</td>
</tr>
<tr>
<td>1994</td>
<td>Johnson et al. (17)</td>
<td>8</td>
<td>all q 14 d</td>
<td>6</td>
<td>4/8 (50%) (&lt; 60 nmol/l and il &gt; 60 µg, &lt; 30 nmol/l)</td>
<td>7/8 (88%) (&lt; 10 mU/l)</td>
<td>63</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1994</td>
<td>Marek et al. (18)</td>
<td>13</td>
<td>all q 14 d</td>
<td>9–19</td>
<td>3/13 (23%) (&lt; 270 µg/l)</td>
<td>3/13 (23%) (&lt; 5 µg/l)</td>
<td>100</td>
<td>NA</td>
<td>42</td>
<td>NA</td>
</tr>
<tr>
<td>1994</td>
<td>Morange et al. (19)</td>
<td>19</td>
<td>q 14 d, n = 9</td>
<td>6</td>
<td>13/19 (68%) (&lt; 2.5 µU/l)</td>
<td>17/19 (88%) (&lt; 5 µg/l)</td>
<td>16</td>
<td>11</td>
<td>none</td>
<td>16**</td>
</tr>
<tr>
<td>1995</td>
<td>Caron et al. (20)</td>
<td>9</td>
<td>q 14 d, n = 6</td>
<td>6</td>
<td>7/9 (78%) (&lt; 35 nmol/l)</td>
<td>7/9 (78%) (&lt; 5 µg/l)</td>
<td>11</td>
<td>67</td>
<td>none</td>
<td>33**</td>
</tr>
<tr>
<td>1996</td>
<td>al-Maskari et al. (21)</td>
<td>10</td>
<td>q 14 d, n = 5</td>
<td>6</td>
<td>5/10 (50%) (&lt; 60 nmol/l and il &gt; 60 µg, &lt; 30 nmol/l)</td>
<td>6/10 (60%) (&lt; 5 mU/l)</td>
<td>most</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1996</td>
<td>Caron et al. (23)</td>
<td>22</td>
<td>q 14 d, n = 13</td>
<td>6–36</td>
<td>14/22 (64%) (&lt; 300 µg/l)</td>
<td>6/22 (27%) (&lt; 2.5 µg/l)</td>
<td>59</td>
<td>18</td>
<td>none</td>
<td>25</td>
</tr>
<tr>
<td>1996</td>
<td>Giusti et al. (22)</td>
<td>57</td>
<td>q 14 d, n = 37</td>
<td>6</td>
<td>19/50 (38%) (&lt; 366 µg/l)</td>
<td>26/48 (54%) (&lt; 5 µg/l)</td>
<td>54</td>
<td>5</td>
<td>12***</td>
<td>NA</td>
</tr>
<tr>
<td>1999</td>
<td>Colao et al. (24)</td>
<td>45</td>
<td>q 14 d, n = 25</td>
<td>6</td>
<td>26/45 (58%) (normal for age)</td>
<td>26/45 (58%) (&lt; 2.5 µg/l)</td>
<td>27</td>
<td>0</td>
<td>none</td>
<td>5</td>
</tr>
<tr>
<td>1999</td>
<td>Verhelst et al. (this paper)</td>
<td>66</td>
<td>q 14 d, n = 34</td>
<td>12</td>
<td>29/66 (44%) (normal for age)</td>
<td>30/66 (45%) (&lt; 2.5 µg/l)</td>
<td>62</td>
<td>27</td>
<td>9</td>
<td>36</td>
</tr>
</tbody>
</table>

* Usually in small subgroup of patients; ** patients with tumor shrinkage under previous octreotide therapy included; *** 7 drop-outs excluded from the analysis (total of 57 patients); **** including non-compliance and ineffectiveness. NA = not available; GI, gastrointestinal; y, year; q 14 d, every 14 days.
injections seem to be better tolerated with only 7.5% of patients having pain at the injection site (28). Nevertheless, almost all patients preferred the lanreotide SR injections to the daily subcutaneous form, underlining that this regimen considerably improved their quality of life.

Effects on tumor volume seemed difficult to judge, similar to the experience in other studies (Table 1), but a small reduction might be seen in up to one third of patients.

In agreement with other trials with lanreotide SR (16, 22, 25), we observed a small rise in fasting blood glucose during therapy, whereas others found no change in glucose metabolism (23). In our study, as well as in others (22, 23), no obvious deterioration in glucose metabolism was seen in patients with overt diabetes.

This study in a large number of patients confirms lanreotide SR as an effective, well-tolerated somatostatin analog for the treatment of acromegaly. Compared with subcutaneous octreotide it improves considerably the patient’s comfort. Both drugs seemed to be equally effective, but some patients who obtained a normal IGF-I with subcutaneous octreotide were not controlled with lanreotide SR and vice versa. In almost half the patients, the interval between the intramuscular injections was increased from once every 14 days to once every 10 or 7 days.

Acknowledgements
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