CLINICAL STUDY

Optimalization and cost management of lanreotide-Autogel therapy in acromegaly

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Abstract

Background: Lanreotide-Autogel is a depot formulation of the somatostatin analog lanreotide used in the treatment of acromegaly. We investigated whether prolonging or shortening the interval between injections would offer any benefit.

Subjects and methods: The interval was prolonged from once every 4 weeks to once every 6 weeks when patients (n=9) had normal IGF-I and GH concentrations. When patients (n=12) had still elevated IGF-I or GH on the maximal dose of 120 mg every 4 weeks, the interval was shortened to once every 3 weeks. Serum IGF-I and GH were measured after 12 and 24 weeks to allow for dose adaptation. Symptoms and tumor volume were evaluated at baseline and after 36 weeks.

Results: In seven of the nine subjects with normal IGF-I and GH, the interval could be extended to 6 weeks without losing efficacy on IGF-I (195 vs 213 μg/l; not significant, NS) and GH concentrations (1.4 vs 1.3 μg/l; NS). The weekly dose could significantly be reduced (from 23.3 to 17.8 mg; P=0.002). In only 1 of the 12 not-controlled patients, reducing the interval to once every 3 weeks induced normalization of IGF-I and GH.

Conclusion: In subjects whose acromegaly is well controlled using lanreotide-Autogel, prolonging the time interval between injections can often be increased 4 to 6 weeks without loss of efficacy, thereby improving the subject’s comfort and reducing the cost of treatment. On the other hand, in subjects whose acromegaly is not controlled on a dose of 120 mg every 4 weeks, reducing the interval to every 3 weeks is rarely beneficial.

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Introduction

Uncontrolled acromegaly is associated with significant morbidity and mortality (1). The main goal of therapy is to normalize, or at least adequately control, both biochemical disease markers, insulin-like growth factor-I (IGF-I) and growth hormone (GH), allowing reversal of the mortality rate into the range of the general population. Although neurosurgery is still considered the first-line treatment for acromegaly, the cure rate in the best surgical series is estimated to be not higher than 80–90% for microadenomas and 30–50% for macroadenomas (2, 3). Therefore, adjuvant therapy is frequently necessary to achieve optimal IGF-I and GH control (1). External radiotherapy usually prevents tumor growth and reduces IGF-I and GH levels, but the slow onset of action, the high incidence of hypopituitarism, and the cerebrovascular complications have minimized its role (4–6). Recent advances in the development of pharmacologic agents have permitted more efficacious medical treatment of persistent acromegaly, and these agents are also emerging as compelling options for primary therapy in selected patients (7). However, due to its long-term requirement, medical therapy has an elevated financial burden, compared with uneventful surgery or radiotherapy. Cabergoline, a long-acting dopamine agonist, appears to have a particular benefit in acromegalic patients with moderate disease activity or a tumor co-secreting prolactin (8, 9). Long-acting somatostatin analogs, such as octreotide and lanreotide, exhibiting a high affinity for somatostatin analog long acting (SSTR)-2, have been shown to be effective, normalizing serum IGF-I levels in up to 60% of unselected cases (10–16). The GH receptor antagonist, pegvisomant, is presently the most effective medical treatment, normalizing IGF-I secretion in about 90% of cases (17). Restraints for this treatment are the need of frequent injections and the high cost, specially if reimbursement is not provided by the social security. The limitations of the medical therapies have led investigators to develop combined drug modalities (18, 19) and to look for somatostatin analogs with improved SSTR-5 binding or with binding to the dopamine receptor (20, 21).

In this study, we first investigated whether cost reduction of somatostatin analog treatment could be achieved by prolonging the time interval between injections without loss of efficacy in patients whose
acromegaly is adequately controlled by lanreotide-Autogel. Secondly, we considered the possibility of enhancing the efficacy of lanreotide-Autogel by increasing the dose. For these purposes, the dose of lanreotide-Autogel was adapted to optimize the treatment and to reduce the cost in a group of 21 acromegalic patients already receiving a 4-weekly dose of this medication for a period of 24 weeks.

Subjects and methods

Subjects and study protocol

Of the 25 subjects with active acromegaly reported in a previous study comparing the efficacy of octreotide-LAR and lanreotide-Autogel (16), 21 were included in this prospective, open, multicenter, within-subject controlled extension study. All subjects had been treated during the 12 previous weeks with lanreotide-Autogel at a fixed 4-weekly dose of 60 mg (n = 3), 90 mg (n = 3), or 120 mg (n = 15). The dose titration in this study depended upon the measurements of age- and gender-adjusted IGF-I values and the mean of three consecutive GH determinations taken at 30-min intervals. At the start of this study, a first dose adaptation was carried out. The time interval between two injections was increased to 6 weeks in patients whose acromegaly is well controlled overall (arbitrarily defined by a normal IGF-I and a mean GH < 1.7 μg/l). In patients with overall poor control (IGF-I above normal and GH > 2.5 μg/l), the starting dose was increased by 30 mg to a maximum of 120 mg every 4 weeks or the time interval was decreased to 3 weeks in patients in whom the 120 mg dosage was already used. In case of 'reasonably good' control (IGF-I normal and mean GH > 1.7 μg/l), the time interval was increased to 6 weeks and the dose was simultaneously increased by 30 mg, resulting in a comparable weekly dose. After periods of 12 and 24 weeks from baseline, a further dose adaptation was done in cases of poor control, by increasing the dose or by decreasing the time between injections.

The analysis at the end of the study was performed by taking into account the efficacy of the final dose of lanreotide-Autogel. For the purpose of comparison, the dose is reported in milligrams per week regardless of the frequency of administration. The subjects were separ-ated into two groups: group A consisted of nine subjects receiving a final dose of lanreotide-Autogel ≤ 30 mg per week (classical dose group) and group B consisted of 12 subjects in whom the dose of lanreotide-Autogel had to be increased to 40 mg per week because of inadequate IGF-I and GH control with a classical dose. In each group, we compared the IGF-I and GH values and the doses of lanreotide-Autogel used at the start of the study (baseline) and at 36 weeks (final). Characteristics of both groups are given in Table 1. Only small differences between both groups were observed regarding gender - distribution, age, BMI, blood pressure, duration of

GH and IGF-I measurements

All fasting IGF-I and GH measurements were performed centrally by automated, two-site chemiluminescence immunoassays (Nichols Advantage IGF-I Assay and Nichols Advantage HGH Assay, Nichols Institute Diagnostics, San Juan Capistrano, CA, USA).

The sensitivity of the IGF-I assay was 6 μg/l and the intra- and inter-assay coefficients of variation were 5.2 and 5.7% respectively. The age-related normal serum IGF-I concentrations were 125–379 μg/l (25–30 years), 114–316 μg/l (30–35 years), 108–301 μg/l (35–40 years), 101–279 μg/l (40–50 years), 92–253 μg/l (50–60 years), and 83–230 μg/l (60–80 years).

The calculated sensitivity of the GH assay was 0.1 μg/l and the intra- and inter-assay coefficients of variation were 4.8 and 5.8% respectively. GH values were expressed in terms of the first WHO International Standard (IS) 80/505 for rDNA GH, in use at the time of the assay (conversion factor for expression in terms of the second WHO IS 98/574 provided by Nichols=GH concentration×0.56).

Most studies in treated acromegalis are using a 2.5 ng/ml threshold as a ‘safe’ GH level but emerging evidence exists that this limit might be too high and should be decreased to 2.0 ng/ml or even lower. We arbitrarily chose 1.7 ng/ml as strict cutoff value of good control. In contrast, a GH value above 2.5 μg/l was considered as indicative of poor control.

Symptoms of acromegaly

Five signs or symptoms of active acromegaly (headache, perspiration, asthenia, swelling of extremities, and joint pain) were self-evaluated by the subject using a four-point rating scale (absent = 0, mild = 1, moderate = 2, and severe = 3). A comparison between the symptomsology at the start and end of the study is reported.

Cost of treatment

The cost of one injection of lanreotide-Autogel in Belgium is € 943 for 60 mg, € 1128 for 90 mg, and € 1380 for 120 mg.
Table 1 Clinical and biochemical characteristics of acromegalic patients grouped according to response to lanreotide-Autogel at baseline and after dose adaptation.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P (A versus B)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Final</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (gender)</td>
<td>9 (5 M + 4 F)</td>
<td>12 (6 M + 6 F)</td>
<td>NS</td>
</tr>
<tr>
<td>Age at analysis (years, mean ± s.d.)</td>
<td>54.6 ± 13.1</td>
<td>49.2 ± 16.2</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m², mean ± s.d.)</td>
<td>26.8 ± 3.3</td>
<td>28.7 ± 4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure (mmHg, mean ± s.d.)</td>
<td>124/76 ± 10/9</td>
<td>129/84 ± 20/11</td>
<td>NS</td>
</tr>
<tr>
<td>Time span since diagnosis (years, mean ± s.d.)</td>
<td>10.4 ± 5.0</td>
<td>7.3 ± 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Tumour size</td>
<td>8 macro/1 micro</td>
<td>1 macro</td>
<td>NS</td>
</tr>
<tr>
<td>Surgery performed (n)</td>
<td>2</td>
<td>8</td>
<td>0.04</td>
</tr>
<tr>
<td>Time span since surgery (years, mean ± s.d.)</td>
<td>5.0 ± 0.0</td>
<td>8.5 ± 7.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Radiotherapy performed (n)</td>
<td>1</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Time span since radiotherapy (years, mean ± s.d.)</td>
<td>22.0</td>
<td>7.7 ± 5.0</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of somatostatin therapy (months, mean ± s.d.)</td>
<td>33.9 ± 21.1</td>
<td>23.0 ± 10.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Lanreotide-Autogel weekly dose (mg, mean ± s.d.)</td>
<td>23.3 ± 7.0</td>
<td>17.8 ± 7.9*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GH (μg/l, mean ± s.d.)</td>
<td>1.4 ± 1.6</td>
<td>3.3 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>IGF-I (μg/l, mean ± s.d.)</td>
<td>195.6 ± 68</td>
<td>444 ± 220</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl, mean ± s.d.)</td>
<td>114 ± 24</td>
<td>110 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (% mean ± s.d.)</td>
<td>6.2 ± 0.9</td>
<td>5.9 ± 0.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Signs of active acromegaly (points, mean ± s.d.)</td>
<td>2.2 ± 2.2</td>
<td>2.8 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>General side effects of Autogel (points, mean ± s.d.)</td>
<td>0.4 ± 0.5</td>
<td>0.4 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Local side effects of Autogel (points, mean ± s.d.)</td>
<td>0.1 ± 0.3</td>
<td>0.3 ± 0.8</td>
<td>0.02</td>
</tr>
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NS, not significant; NA, not applicable; *P=0.002 between baseline and final; †P<0.001 between baseline and final.

As could be assumed from the subdivision, the two groups showed significantly distinct characteristics regarding the weekly dose of lanreotide-Autogel. The clinical signs of acromegaly, although not in a significant manner, lanreotide-Autogel was well tolerated since general and local side effects were scarce in both groups (Table 1).

Results

Continuous normally distributed variables were analyzed using an ANOVA model to compare the start and end of the study. For continuous variables which even after log transformation grossly violated the normality assumption, the Wilcoxon signed-rank test was performed on the recorded differences between the start and end of the study. Changes in tumor size were defined as absent (≤25%), moderate (25%–50%), or marked (≥50%).

Safety

General adverse side effects of lanreotide-Autogel (nausea, vomiting, and diarrhea) and local effects (pain, erythema, and induration at the injection site) were recorded throughout the study. Ultrasound examination of the gallbladder was performed at the start and end of the study. Serum lipase levels were measured at the start and end of the study. The volume of the tumor was calculated using the mathematical formula of a rotating ellipsoid (34).

Continuous variables which after log transformation grossly violated the normality assumption were analyzed using an ANOVA model to compare in the same way.
The calculated weekly dose of lanreotide-Autogel could be significantly decreased from 23.3 ± 7.0 to 17.8 ± 7.9 mg (P = 0.002). This had no significant impact on IGF-I concentration (195 ± 68 vs 213 ± 31 µg/l before and after dose adaptation respectively; NS), nor on mean GH concentration (1.4 ± 1.6 vs 1.3 ± 0.8; NS).

The individual doses of lanreotide-Autogel and the IGF-I and GH responses are shown in the left panels of Figs 1 and 2 (IGF-I and GH respectively).

Nine subjects were ultimately controlled for IGF-I and GH concentrations with a weekly dose of lanreotide-Autogel equal or ! 30 mg. All nine subjects had already a normal IGF-I and seven had a safe GH value at baseline. One of the subjects with a slightly elevated GH concentration (A4) showed normalization without increasing the dose lanreotide-Autogel, while the dose could even be decreased in another one (A6). Overall, the weekly dose could be diminished in seven of nine subjects by prolonging the time interval between injections to 6 weeks without deteriorating the biochemical control of acromegaly.

Plasma glucose and HbA1c were not different from baseline (Table 1). The clinical signs of active acromegaly decreased from 2.2 ± 2.2 at baseline to 1.0 ± 1.0 at the end of the trial (NS). No significant changes in general or local side effects occurred during the study, except for a major local irritation in one subject. The number of subjects with gallstones increased from four to five. Pituitary imaging performed in seven subjects showed a moderate decrease in tumor volume in one and no changes in the remainder.

On a yearly basis, for seven of the nine subjects in whom the dose could be decreased the cost diminished by almost 34 000 € from 137 865 € to 103 870 €.

**Dose adaptation in group B (no disease control – high dose)**

The weekly dose of lanreotide-Autogel, which was adapted in all subjects (B1–12), increased significantly from 30 to 40 mg (P < 0.001). Despite this adaptation, further, although not-significant increases, in IGF-I (444 ± 220 vs 479 ± 220 µg/l) and GH concentrations (4.1 ± 2.6 vs 5.0 ± 4.7 µg/l) were observed.

The individual doses of lanreotide-Autogel and the IGF-I and GH responses are shown in the right panels of Figs 1 and 2 (IGF-I and GH respectively).

Increase of the lanreotide-Autogel dose to 40 mg per week resulted in a normalization of both IGF-I and GH in only one subject (B9). One subject (B4) normalized GH levels without normalization of IGF-I. One subject (B11) with normal IGF-I before and after dose adaptation still maintained elevated GH levels despite this adaptation. One subject (B10) with safe GH before and after dose adaptation still maintained elevated IGF-I levels despite this adaptation. IGF-I control was lost in one subject (B3) and GH control in another one (B12). In the remaining six subjects, normalization of IGF-I or GH did not occur.

Plasma glucose and HbA1c were not different from baseline. The clinical signs of active acromegaly increased from 2.8 ± 2.6 at baseline to 3.6 ± 3.1 at the end of the trial (NS). No major changes in general and local side effects occurred. The number of subjects with gallstones increased from five to six. Pituitary imaging performed in seven subjects showed a moderate reduction in volume in two and an increase moderate in another two.

The yearly cost for the 12 subjects in this study receiving a 4-weekly dose of 120 mg lanreotide-Autogel
would increase by € 71,760 from € 215,280 to € 287,040 if the dose were given 3-weekly, however it was only beneficial for one subject.

Discussion

Somatostatin analogs such as octreotide and lanreotide are acceptable therapeutic options in acromegaly since they are known to normalize IGF-I and GH levels in 40–60% and to induce some tumor shrinkage in 30% of subjects (10, 11). These drugs are available in depot preparations in different dosages, 20–30 mg for octreotide-LAR and 60–90–120 mg for lanreotide-Autogel. The interval between injections is usually kept constant at 4 weeks. It is generally advised to regularly adjust the dose upon the serum IGF-I and GH levels in order to obtain the best effect on disease activity at the lowest price. We arbitrarily chose 1.7 ng/ml as strict cutoff value of control of disease because several retrospective studies have reported that a GH value of 2 mg/l or even lower is an appropriate therapeutic target, as values above this level are associated with increased mortality (31).

In the present study, which was an extension of a comparison study between octreotide-LAR and lanreotide-Autogel (16), we investigated whether changes in the interval between lanreotide-Autogel injections in addition to changes in the dose would offer any benefit in terms of clinical and biochemical control, subject’s comfort, and cost of therapy. We could first demonstrate that in 78% of subjects, well controlled by the classical dose of 30 mg/week or less (good responders), the interval between injections of lanreotide-Autogel could be extended to 6 weeks instead of 4 weeks without significant loss in disease control. In addition, the total dose of medication could be significantly reduced from 23.3 to 17.8 mg/week. But even when the total weekly dose remains unchanged, prolonging the interval between injections can improve patient comfort and reduce costs. For instance, changing to dose lanreotide-Autogel from 60 mg every 4 weeks to 90 mg every 6 weeks results in a decrease of the yearly number of injections from 12 to 8 and in a reduction of the yearly cost from 11,316 € to 9024 €, due to the lower relative price of the 90 mg dosage.

The possibility of extending the interval between injections of somatostatin analogs was also reported in studies with lanreotide prolonged release, another depot form of lanreotide which is released gradually over 7–14 days after injection via biodegradable microparticles. In one study, it was shown that 27% of patients with acromegaly still had safe GH levels 3 weeks after their last injection, suggesting that the interval may be increased from once every 1 or 2 weeks to once every 3 weeks when subjects initially respond well (22). In another study, the interval between injections could even be increased to once every 4 weeks in lanreotide-sensitive subjects, without altering the efficacy upon IGF-I and GH secretion (23). More recently, a large number of acromegalic subjects switched from lanreotide prolonged release to lanreotide-Autogel could remain well controlled with injections every 6 or even 8 weeks, at the condition that they were well controlled by lanreotide prolonged release every 10–14 days (24). The possibility of extending the interval between injections from once every 4 to once every 6 weeks or even longer without loosing efficacy has also been reported with octreotide-LAR (22, 25, 26).
of 12 months of treatment with lanreotide-Autogel, a true steady state was still not clearly obtained in some of our patients. Several studies have shown indeed that serum GH and IGF-I levels may continue to progressively decline during long-term treatment with somatostatin analogs (32, 33).

The reasons why IGF-I and GH levels remain under control after prolonging the interval are probably twofold. First, in a pharmacodynamic study in 24 healthy volunteers, significant levels of lanreotide could still be found at day 56, indicating continued drug activity beyond 4 weeks (27). Second, IGF-I and GH levels once adequately suppressed with somatostatin analogs may need 4–12 weeks before starting to rise again (28).

In the second part of the present study, we examined whether shortening the dose interval of lanreotide-Autogel would offer any advantage in terms of control of IGF-I and GH levels in subjects not controlled by the classical dose of 120 mg 4-weekly. Despite increasing the weekly dose from 30 to 40 mg, only one of the subjects (8%) experienced any benefit from reducing the interval between injections to 3 weeks. The clinical experience with high-dose somatostatin analogs remains limited, but, similarly to lanreotide-Autogel, a poor therapeutic response with octreotide-LAR has been observed. Seven acromegalic subjects, included in a series of 36 treated by octreotide-LAR, received a monthly dose of 40 mg, but only one achieved a normalization of IGF-I and a safe GH concentration (29). These findings concur with the concept that partial or complete resistance of somatotrope adenomas to somatostatin analogs is usually not related to inadequate dosing but rather to a deficient number or insensitive type of receptors on the cell membrane (30).

In conclusion, this open multicenter study shows that in well-controlled subjects prolonging the time interval between two injections of lanreotide-Autogel from 4 to 6 weeks can be done in a majority of subjects without losing efficacy, thereby improving their comfort and reducing the cost of treatment. On the other hand, in not-controlled subjects on the maximal dose of 120 mg 4-weekly, a further increase of the dose will rarely improve the biochemical control.

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References


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