Abstract

Background: Somatostatin analogs (SA) have been used for over 25 years in the treatment of acromegaly. A major disadvantage is the need to continue therapy indefinitely.

Objective: To evaluate the feasibility of discontinuing therapy in well-controlled patients with acromegaly treated chronically with SA.

Design and methods: Of the 205 subjects on octreotide LAR, we selected those who met the following criteria: two or more years of treatment, a stable dose and injection interval of 20 mg every 8 weeks or longer for the previous year, no history of radiation, no cabergoline for the previous 6 months, a GH < 1.5 ng/ml, and an IGF1 < 1.2× upper limit of normal (ULN). Octreotide LAR was stopped and both GH and IGF1 were measured monthly for 4 months; a glucose-suppressed GH value and magnetic resonance imaging were obtained at the 4th month, thereafter, basal GH and IGF1 were measured q. 3 months, for 12–18 months. Patients were removed from the study if GH or IGF1 rose to 1.5 ng/ml or 1.2× ULN respectively.

Results: Twelve patients (ten women, mean age 48 ± 13 years) were studied. Seven patients (58.3%) relapsed biochemically within 1 year of having stopped the SA; two patients relapsed by GH and IGF1 criteria, the remaining five patients kept GH levels within target. Five patients (41.7%) remain in remission after 12 months of follow-up. Non-recurring patients were on longer injection intervals but no other characteristic was associated with a successful withdrawal.

Conclusion: Withdrawal of SA is possible in a small but distinct subset of patients, particularly in those who are very well controlled on relatively low doses administered at long intervals.

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Introduction

Acromegaly is a chronic disease caused in over 98% of the cases by a pituitary adenoma (1). The treatment of choice is transsphenoidal resection of the tumor (2); however, in the most experienced centers, this therapeutic option is far from perfect. While some 80–90% of microadenomas and confined intrasellar macroadenomas can be cured by surgery, larger and more invasive lesions can be successfully removed in <40% of the cases (3, 4). Thus, a considerable proportion of patients require adjunctive forms of therapy after surgery, be it pharmacological treatment with somatostatin analogs (SA), GH receptor antagonists or dopamine agonists (DAs), either alone or in different combinations, or radiation therapy in any of its modalities. In addition, primary pharmacological treatment of acromegaly, particularly with SA, is increasingly being used in patients with medical contraindications for surgery or whose tumors are considered inoperable (1, 5). SA (octreotide and lanreotide) are the most frequently used drugs and have been available for over 25 years (6) with reported efficacies in terms of achieving both, a normal insulin-like growth factor 1 (IGF1) and a ‘safe’ GH level, that varies between 30 and 60% (7–11). The depot formulations of both octreotide (octreotide LAR, Sandostatin LAR) and lanreotide (lanreotide autogel, Somatuline Depot) are usually administered every 4 weeks, at least initially. However, in patients who respond, the injection interval can be increased to every 6, 8 or even 10, or more weeks, resulting in significant cost savings and increased patient convenience (12, 13).

One of the major drawbacks of SA therapy is the apparent need to continue it indefinitely. Therefore, being able to discontinue SA in some patients with acromegaly, analogous to the situation in patients with prolactinomas treated with DA (14, 15), is an attractive theoretical possibility. Based on the observations mentioned above, we hypothesized that in a subset of patients with acromegaly who respond extremely well to SA, as reflected by an excellent biochemical
control with relatively low doses, such agents may cause irreversible functional changes in GH release and might therefore be stopped after several years of treatment.

Materials and methods

Patients

All patients were recruited from the Acromegaly Clinic, at the Hospital de Especialidades, Centro Médico Nacional S.XXI in Mexico City. This Clinic has a database of 457 patients that have been followed for 12 years. Two hundred and five of these 457 patients (45%) have been receiving pharmacological therapy with octreotide LAR (some as their primary treatment and some others after failed pituitary surgery) for 8 months to 8 years. The doses are regularly reviewed and the patients weaned down to the lowest dose at the longest interval compatible with good biochemical control (Fig. 1). The dosages vary as follows: 9% is on 40 mg every 4 weeks, 59% on 20 mg every 4 weeks, 11% on 20 mg every 6 weeks, 8.5% on 20 mg every 8 weeks, 8.5% on 20 mg every 10 weeks, and 4% on 20 mg every 12 weeks (Fig. 1). All 205 patients are considered to be biochemically controlled, having achieved a basal GH of 1.5 ng/ml and an IGF1 level 1.2×upper limit of normal (ULN); one-third of the cohort receives combination therapy with cabergoline at doses that range between 1 and 2 mg/week.

Study design and selection criteria

We selected only those patients who met the following criteria: i) having been on octreotide LAR for at least 2 years with a stable dose for the previous year, ii) an injection interval of 8 weeks or longer, iii) complete biochemical control defined by a basal GH <1.5 ng/ml and an IGF1 <1.2×ULN, iv) no history of radiation therapy, v) a tumor remnant 8 mm in its largest diameter on a recent (<3 months) magnetic resonance imaging (MRI), and vi) no history of DA use in the previous 6 months (Fig. 2). The protocol was approved by our Local Ethics and Scientific Committees and all patients gave written informed consent. After receiving their last octreotide LAR injection, patients were instructed to continue their usual medications, including the ones used for pituitary hormone replacement, and to register any changes in symptoms and signs. Patients were asked to return to the clinic at 0800 h every month for a full clinical assessment and blood sampling for the whole duration of the study. A single GH and IGF1 were measured monthly for the first 3 months, while on the 4th month an oral glucose tolerance test with a 75 g glucose load was performed, measuring GH at 30, 60, 90, and 120 min; serum IGF1 was also measured in the basal sample. If at any of the monthly measurements either the GH or the IGF1 rose to >1.5 ng/ml or >1.2×ULN, respectively, the patient was discharged from the study and returned to his/her previous octreotide LAR dose regimen. Those patients, whose GH and IGF1 remained within the established biochemical goals, were followed monthly as noted above for at least 12 months.

Hormone assays

Both GH and IGF1 values are expressed in mass units. To convert to SI units, multiply by 0.13 in the case of IGF1 and by two in the case of GH. GH was measured using a two-site chemiluminescent enzyme assay (DiaSorin-Liaison, Salugia, Italy), with a detection limit of 0.009 ng/ml and intra- and inter-assay coefficients of variation (CV) of 2.5 and 5.8%, respectively; the International Reference Preparation (IRP) used in the calibration of the GH assay was WHO second 95/574. IGF1 was separated from its binding proteins by means of an acid–ethanol extraction step, and the hormone levels were quantified in the extracted samples by a chemiluminescent assay (DiaSorin-Liaison), with advertised intra- and inter-assay CV of 3.8 and 5.5%, respectively; the IRP used in the calibration of the IGF1 assay was WHO second 02/254. We established our own normative IGF1 data analyzing serum samples from 340 healthy individuals and thus calculated the real intra- and inter-assay CV as 3 and 4% respectively. The resulting normal age-adjusted reference values are as follows: 18–30 years, 150–430 ng/ml; 31–40 years, 110–310 ng/ml; 41–50 years, 78–200 ng/ml; 51–60 years, 60–170 ng/ml; 61 and older, 60–150 ng/ml. The other hormonal determinations were carried out using a myriad of commercially available assays.

Statistical analysis

Quantitative data are presented as either means ± s.d. or medians with interquartile ranges, depending on whether the data distribution was normal or not. Normality of data distribution was ascertained by the
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(41.7%) remain in remission after a minimum follow-up

at the 10th and 12th months respectively. Five patients

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weeks, and three every 12 weeks. As for comorbidities,

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tumor was a small intrasellar macroadenoma and at the

beginning of the study only three had visible remnants

on MRI. The mean duration of preceding octreotide
treatment was 4.5 ± 1.2 years. All were on octreotide

LAR 20 mg injections: three every 8 weeks, six every 10

weeks, and three every 12 weeks. As for comorbidities,
one was diabetic, four were glucose intolerant, and three

were hypertensive.

Seven patients (58.3%) relapsed within 1 year of

having stopped the SA; two did so at the 3rd month, one

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of the patients experienced any worsening of acrome-
galy related symptoms such as joint pain, hyperhidrosis,

headaches, or fatigue. No tumor regrowth was

registered in any patient and those subjects with glucose

abnormalities or hypertension did not experience any
deterioration of these comorbidities. Of the seven

patients showing biochemical recurrence, only two did

so by increasing both their GH and IGF1 concentrations

above the criterion levels; the remaining five recurred

only by IGF1 criteria.

Baseline characteristics at diagnosis, including age,
gender distribution; GH and IGF1 levels and tumor
diameter were not different between recurrent and non-

recurrent patients (Table 2). Median GH nadir post-
glucose at the 4th month of follow-up in the whole
group was 0.9 ng/ml (interquartile range 0.17–0.9).

Excluding the two patients who relapsed at the 3rd and

4th months, the median GH nadir post-glucose in the

recurrent group tended to be higher than that in the

non-recurrent group, although this did not reach

statistical significance (recurrent: 0.9 ng/ml (interquar-
tile range 0.4–1.3) and non-recurrent: 0.20 ng/ml

(interquartile range 0.14–0.9), P = 0.40). At the

beginning of the study, three out of seven recurring

patients and none of the five non-recurring patients had

evidence of a tumor remnant on MRI (P = 0.09; Table 1).

On the other hand, three out of five subjects

who remained in remission but none of the seven who

recurred was on octreotide LAR injection intervals of

0.70 vs 1.32, respectively , P = 0.003). GH was similar

between the groups (median GH 1.10 vs 1.02 ng/ml,

recurrent and non-recurrent, respectively, P = 0.60),

reflecting the fact that many patients who recurred did

so only by IGF1 criteria (Table 2). A stratified analysis

including clinical, imaging, and biochemical character-

istics, at diagnosis and at the beginning of the study,

failed to identify any factor that could predict successful

withdrawal of the SA.

Results

Twelve patients (ten women and two men) met the

selection criteria and thus were recruited for the study;

Table 1 depicts their individual baseline characteristics.

Their mean age was 48.4 ± 13.4 years (range 25–65),

and all but one were on octreotide LAR after failed

pituitary surgery. In over 60% of them the original

tumor was a small intrasellar macroadenoma and at the

beginning of the study only three had visible remnants

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Table 1 Individual baseline features at diagnosis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>GH (ng/ml)</th>
<th>IGF1 (× ULN)</th>
<th>Largest tumor diameter (cm)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>46</td>
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<td>F</td>
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<td>F</td>
<td>47</td>
<td>81</td>
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<td>2.0</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>47</td>
<td>24.6</td>
<td>2.1</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
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<td>F</td>
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<td>F</td>
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<td>2.14</td>
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</tr>
<tr>
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<td>F</td>
<td>33</td>
<td>21.1</td>
<td>1.67</td>
<td>0.6</td>
</tr>
<tr>
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<td>F</td>
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<td>2</td>
<td>2.46</td>
<td>0.5</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>44</td>
<td>5</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>19</td>
<td>5.1</td>
<td>2.03</td>
<td>1.0</td>
</tr>
</tbody>
</table>
These two studies occurred at the beginning of the depot controlled GH and IGF1 after 6 months of follow-up. Taken off octreotide, of whom only one remained with reported on seven well-controlled patients who were at the end of the follow-up period. Lorcy included in the study.

Earlier attempts to stop SA treatment in patients with acromegaly have been made. Stewart et al. (16) studied about 200 patients on SA treatment, we identified 12 (6%) whom we deemed possible candidates for long-term remission. Five of the 12 patients (41.3%) included in the study remain with normal IGF1 levels and very well controlled GH concentrations after at least 12 months of follow-up. Importantly, no patient in the study developed any worsening of symptoms or comorbidities associated with acromegaly, and MRI evaluation did not show tumor regrowth. Neither GH nor IGF1 levels at diagnosis, nor those at the beginning of the study were associated with the likelihood of remaining on remission after stopping SA therapy. The only baseline parameter that seemed to be associated with a successful withdrawal was a long injection interval; patients who remained in remission were those who required lower doses of octreotide LAR. Although more patients in the recurring group had evidence of a tumor remnant on the baseline MRI than the non-recurring group, this did not reach statistical significance, perhaps due to the small number of subjects included in the study.

Earlier attempts to stop SA treatment in patients with acromegaly have been made. Stewart et al. (16) studied 12 octreotide-treated patients in whom they withheld the SA for up to 4 months; only two remained controlled at the end of the follow-up period. Lorcy et al. (17) reported on seven well-controlled patients who were taken off octreotide, of whom only one remained with controlled GH and IGF1 after 6 months of follow-up. These two studies occurred at the beginning of the depot SA era and were not specifically designed to evaluate whether withholding therapy was feasible.

Recently, Ronchi et al. (18) attempted SA suspension in 27 patients with acromegaly who had been successfully treated with octreotide or lanreotide for several years. In this multicenter study, only nine of the 27 patients (33.3%) were able to sustain a long-term remission after SA withdrawal (18). In contrast to our results, these authors found that those subjects who remained in remission had lower IGF1 levels while being treated with either octreotide or lanreotide. However, several methodological and design differences between this study and our own should be considered. First, we only included patients who were already receiving octreotide LAR at intervals greater than every 8 weeks and who had not been irradiated. Thus, the study population consisted of subjects with a hypothetically reasonable chance of coming off SA treatment, and in whom remission could not have been due to other prior therapeutic interventions such as the delayed effect of radiation therapy. We considered it unnecessary to attempt SA withdrawal in patients who were receiving octreotide LAR injections at intervals of every 6 weeks or less, since most of them had tried unsuccessfully to space up their injection intervals by 2 weeks. Although the patients studied by Ronchi’s et al. (18) were well controlled with a stable dose of either octreotide LAR or lanreotide, no further information regarding such dose (i.e. amount and injection interval) was provided. Secondly, we used very stringent biochemical criteria (basal GH 1.5 ng/ml and IGF1 1.2×ULN) to keep our patients off treatment. Furthermore, of those patients who recurred only two showed both, GH and IGF1 concentrations above the permitted levels, whereas five were removed from the study because they increased their IGF1 concentrations but remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remained with a serum concentration above the permitted levels, whereas five remaine...
GH within the pre-established target. The definition of biochemical control was less strict in the Italian multicenter study since they used a GH cut off value of 2.5 ng/ml (18). If our biochemical criteria had been less stringent, a greater proportion could have remained without treatment, as neither the symptoms, nor the comorbidities of acromegaly deteriorated upon withdrawal. This fact highlights the issue of what our goals when treating an acromegalic patient with SA should be. Certainly, symptomatic relief and control of comorbidities must be high in the priorities list, yet the specific degree of biochemical control continues to be a matter of debate among experts (19). If we accept the notion that SA can successfully control but not cure acromegaly, then the selection of a particular GH or IGF1 cut off value should derive from epidemiological studies that demonstrate that decreasing GH and IGF1 to a particular level results in a significant reduction in the mortality rate of the disease (19–21). The most commonly used ‘safe GH’ value is 2.5 ng/ml, derived from epidemiological studies that measure the hormone with RIAs (20, 21). There is no published mortality data using GH measurements performed by the current ultrasensitive assays; a GH value of 2.5 ng/ml measured by RIA, probably corresponds to a value of 1.5 ng/ml or less when analyzed by an ultrasensitive assay. In spite of this, most clinical trials, even recent ones, measuring GH by ultrasensitive assays assess the efficacy of SA in the treatment of acromegaly by the 2.5 ng/ml ‘safe’ cutoff to define control (9–11).

Both, the anti-secretory and the anti-proliferative effects of SA are dependent on the expression of somatostatin receptors (sst) by the tumor (particularly sst2 and to a lesser extent sst5) (22, 23). Activation of sst1, sst2, sst4, and sst5 results in cell cycle arrest as reflected by a low Ki-67 index and by an increased proportion of cells in G1 and M (24). In keeping with these findings, morphological changes in tumors pretreated with octreotide have not been particularly striking: there is acidophilia and interstitial fibrosis and a moderate reduction in cytoplasmic volume; however, no necrosis is found (25). On the other hand, activation of sst3 and possibly sst2 can induce apoptosis (26). Studies in primary cultures of somatotrophinomas have shown that octreotide exposure in vitro increases the total number of apoptotic cells as reflected by the TUNEL assay and in activation of the caspase cascade as shown by an increment in cleaved CK18 (27). SA may also have anti-angiogenic actions, however, due to the inhibition of growth factors such as VEGF, bFGF, and IGF1 itself (28). The importance of angiogenesis inhibition in the anti-proliferative effect of SA is still controversial (23). Thus, available data suggest that the anti-proliferative effect of SA is more cytostatic than cytotoxic, yet some experimental data leave open the possibility of apoptosis-induction.

Even though a little over 40% of the patients in the study did not recur, looking at the big picture, only 2.4% of all the patients receiving octreotide therapy, were able to come off treatment. Whether the five patients who remain in remission will eventually relapse is difficult to predict although it seems reasonably unlikely. If they remain in remission, then the possibility of a real cytotoxic effect of SA on tumoral somatotrophs should be seriously entertained. We conclude that in patients with acromegaly who are very well controlled on relatively small doses of either octreotide or lanreotide, reducing the dose by progressively increasing the injection interval is a cost-effective strategy. Furthermore, a proportion of these subjects, particularly those who receive their SA at intervals longer than 10 weeks, will be able to stop their medication and remain in long-term remission.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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