CLINICAL STUDY

Preliminary data on biochemical remission of acromegaly after somatostatin analogs withdrawal

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Abstract

Objective: It is still unknown whether prolonged treatment with somatostatin analogs (SSTa) may cause a long-lasting disease remission in GH-secreting adenomas after drug discontinuation. The aim of the present study was to investigate the evolution of GH/IGF-I secretion and tumor mass after SSTa withdrawal in patients affected by acromegaly.

Patients and Design: A total of 27 patients with acromegaly (12 *de novo* and 15 previously operated) were treated with SSTa for a median period of 48 months and considered optimally controlled in hormonal and neuroradiological terms. None of them were previously irradiated.

Methods: Basal GH, post-glucose GH nadir, IGF-I, clinical signs/symptoms, and metabolic parameters were evaluated after 12–16 weeks from drug withdrawal. Only patients who met the current criteria for disease remission remained in drug suspension being periodically re-evaluated for biochemical/clinical data and neuroradiological imaging.

Results: After 12–16 weeks withdrawal, 15 of the 27 patients had disease relapse and restarted SSTa, while 12 were considered 'in disease remission' (44% of total). Glucose metabolism improved in both euglycemic and diabetic patients after short-term SSTa discontinuation. Only one of the ten patients who reached 24 weeks withdrawal showed biochemical disease recurrence. On the whole, five of the patients still in remission after 6 months have already prolonged the follow-up over 12 months (median: 24 months), without clinical and biochemical/neuroradiological evidence of disease recurrence.

Conclusions: These preliminary data indicate a successful withdrawal of SSTa at least in a subset of well-responsive patients with acromegaly and challenge the previously held concept that medical therapy is always a lifelong requirement.

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Introduction

Acromegaly is an insidious disease caused by chronic growth hormone (GH) and insulin-like growth factor-I (IGF-I) hypersecretion prevalently caused by a GH-secreting pituitary adenoma and associated with increased morbidity and mortality (1–3). Premature death is mainly due to a specific cardiomyopathy (4) worsened by the coexistence of several cardiovascular risk factors, such as abnormal carbohydrate metabolism and/or insulin resistance (5, 6). The objectives of treatment include normalization of GH/IGF-I secretion and control of pituitary tumor growth and acromegaly-related comorbidities in order to normalize quality of life and mortality (7). To date, therapeutic options for acromegaly are surgical removal of pituitary adenoma

and/or medical treatment with long-acting somatostatin analogs (SSTa), such as octreotide long-acting release (o-LAR) and lanreotide in both the slow-release formulation (l-SR) and the new Autogel formulation (l-ATG). It is well known that neurosurgery, when successful, normalizes life expectancy in acromegalic patients. Many studies also demonstrated that both primary and secondary prolonged treatments with SSTa are able to induce an enduring GH/IGF-I reduction and a pituitary tumor volume decrease in the majority of patients with acromegaly (8–10). However, to date, it is unknown whether SSTa may also provoke a long-lasting disease remission in GH-secreting adenomas after drug discontinuation, similarly to the definitive cure of prolactinomas frequently induced by dopamine agonists (11, 12).

The aim of the present study was to examine the evolution of GH/IGF-I secretion and tumor mass after drug withdrawal in a selected group of patients with acromegaly characterized by an optimal disease control during chronic treatment with different long-acting SSTa.

Materials and methods

Inclusion and exclusion criteria

The inclusion and exclusion criteria had been discussed *a priori* on a multicenter basis by all three involved Italian Centers (Milan, Naples, and Turin).

Patients with a previous diagnosis of acromegaly were selected along the following inclusion criteria: first, the patients had to be primarily (*de novo*) or secondarily (previously operated on unsuccessfully) treated with different long-acting SSTa for a period of at least 12 consecutive months. All the patients who previously underwent neurosurgery were evaluated for fasting and post-glucose serum GH and IGF-I concentrations two months after their operation. Cases of isolated high IGF-I levels were re-evaluated after 3–4 months to confirm the disease activity before starting eventual SSTa therapy (13). Secondly, the patients had to be considered controlled by SSTa therapy, as indicated by GH levels (mean of at least three samples during saline infusion) $<2.5 \mu\text{g/l}$ and normal IGF-I levels for age (14) at a stable dosage of SSTa for at least nine consecutive months. Thirdly, pituitary tumor or residual tumor volume had to be invisible, reduced, disappeared or at least remained stable at magnetic resonance imaging during SSTa.

The exclusion criterion was previous radiotherapy or radiosurgery.

Patients

Following the inclusion and exclusion criteria, 27 patients with acromegaly (10 males and 17 females, mean age $\pm$ s.d. 57 ± 13 years, body mass index (BMI) $28.0 \pm 3.6 \text{ kg/m}^2$) treated with SSTa for a median period of 48 months (mean: 61 ± 44 months, range: 12–156 months) were recruited for this study. In particular, 11 patients were treated with o-LAR at the dose of 10 ($n=4$), 20 ($n=5$), or 30 mg ($n=2$) every 28 days; 9 with l-SR at the dose of 60 mg every 28 days; and 7 with l-ATG at the dose of 120 mg every 28 ($n=1$), 42 ($n=3$), or 56 days ($n=3$). Twelve patients were primarily treated, while 15 previously underwent unsuccessful neurosurgery. Moreover, 8 patients were euglycemic, 12 had impaired glucose tolerance, and 7 had diabetes mellitus (4 treated with dietetic regimen, 1 with oral drugs, and 1 with combined insulin and oral drug therapy).

Clinical, hormonal, and neuroradiological data of all patients before and during chronic SSTa therapy are summarized in Table 1.

The Local Ethical Committees of the three involved Italian centers approved the protocol study, and patients gave their informed written consent to participate.

Study protocol and assays

The entire study protocol had been previously revised on a multicenter basis.

At the last follow-up visit during chronic SSTa therapy, just before the start of the study, all patients had basal serum GH levels (mean of at least three samples during saline infusion) evaluated by IFMA (AutoDelfia, Wallac OY, Turku, Finland) and serum IGF-I levels by RIA (Mediagnost, Tübingen, Germany), as described previously (15). Acromegaly-related symptoms and signs, such as headache, sweating, paraesthesiae, tiredness, and arthralgia, were investigated and graded 0 (absent), 1 (mild), 2 (moderate), and 3 (severe) by the same observer at each visit and the fourth finger size of left hand by jewellery rings. Neuroradiological investigation was also performed in the same period by the magnetic resonance imaging (MRI) of the pituitary region before and after gadolinium contrast.

All patients underwent a short-term drug withdrawal (12 weeks for o-LAR and l-SR and 16 weeks for l-ATG) and were then re-evaluated for clinical and hormonal parameters, including post-glucose (75 g, oral glucose tolerance test (OGTT)) GH nadir. Patients who simultaneously showed basal GH levels $<2.5 \mu\text{g/l}$, GH nadir $<1 \mu\text{g/l}$, and normal IGF-I concentrations for age (14) prolonged drug suspension with clinical and hormonal re-evaluation every 3 months and MRI every 6 months.

All the patients were also studied for a series of cardiovascular and metabolic parameters during SSTa and every 3 months after drug suspension. Clinical examinations included weight and height with calculation of BMI, systolic and diastolic blood pressure measured according to the World Health Organization International Society of Hypertension Guidelines. Periodical laboratory assessment included fasting and 2-h post-OGTT glucose and insulin levels, glycosylated hemoglobin (HbA1c), total cholesterol, high- and low-density cholesterol, and triglycerides. All these parameters were measured by standard procedures. Basal insulin sensitivity was investigated by the homeostasis model assessment ($\text{HOMA-S\%} = 22.5/\text{fasting insulin (mU/l)} \times \text{fasting glucose (mmol/l)}$) (16). Patients were considered with hypertension and/or dyslipidemia according to ATP III criteria (17), while glucose tolerance was defined according to the new American Diabetes Association (ADA) guidelines (18).

Table 1 Clinical, hormonal, and neuroradiological data of acromegalic patients before and during therapy with different long-acting somatostatin analogs (SSTa).

Patient no.	Sex	TNS	Before SSTa			Type of SSTa	Months of therapy	Age	During SSTa		
			GH (µg/l)	IGF-I (nmol/l)	Tumor mass				GH (µg/l)	IGF-I (nmol/l)	Tumor mass
1	F	Yes	12.0	45	Absent residual	o-LAR	19	66	0.7	18	Absent residual
2	M	Yes	25.0	191	Residual	o-LAR	72	28	0.4	30	Stable
3	M	Yes	5.5	196	Residual	I-SR	72	55	0.2	17	Stable
4	M	No	5.0	55	Macroadenoma	I-ATG	48	64	1.9	33	Stable
5	M	Yes	2.3	52	Absent residual	o-LAR	36	58	1.0	21	Absent residual
6	M	Yes	2.0	63	Absent residual	I-SR	42	68	1.0	39	Absent residual
7	F	Yes	2.6	82	Absent residual	I-SR	60	47	1.7	23	Absent residual
8	F	No	7.7	95	Microadenoma	I-SR	90	73	1.2	14	Disappeared
9	F	Yes	10.0	79	Residual	o-LAR	156	63	0.3	9	Disappeared
10	F	Yes	2.7	69	Absent residual	I-SR	156	68	1.5	20	Absent residual
11	M	No	5.5	67	Microadenoma	o-LAR	24	59	0.6	36	Disappeared
12	F	Yes	8.0	40	Absent residual	I-SR	84	45	1.5	15	Absent residual
13	M	Yes	6.0	81	Residual	o-LAR	36	44	0.7	33	Reduced
14	F	No	6.6	54	Microadenoma	I-ATG	41	48	2.1	28	Reduced
15	F	No	4.0	71	Microadenoma	I-ATG	48	75	0.3	27	Reduced
16	F	No	5.8	67	Microadenoma	I-SR	120	71	1.5	22	ND
17	F	No	8.4	70	Microadenoma	I-SR	12	36	1.7	20	Stable
18	F	Yes	3.1	63	Residual	o-LAR	24	64	0.5	18	Stable
19	M	Yes	3.5	44	Absent residual	o-LAR	18	48	2.0	25	Absent residual
20	F	No	4.0	35	Microadenoma	I-ATG	18	59	0.3	26	Stable
21	M	Yes	1.8	85	Residual	o-LAR	18	35	1.4	26	Stable
22	M	No	9.7	107	Microadenoma	o-LAR	72	56	0.8	38	Disappeared
23	F	No	1.3	47	Microadenoma	o-LAR	92	72	0.2	18	Disappeared
24	F	No	10.2	130	Microadenoma	I-ATG	12	64	1.2	27	Disappeared
25	F	No	17.0	55	Microadenoma	I-ATG	48	42	0.1	17	Reduced
26	F	Yes	8.6	94	Residual	I-ATG	150	62	2.4	22	Reduced
27	F	Yes	9.5	69	Absent residual	I-SR	60	62	0.8	11	Stable

F, female; M, male; TNS, trans-naso-sphenoidal neurosurgery; o-LAR, octreotide long-acting release; I-SR, lanreotide slow release; I-ATG, lanreotide Autogel; ND, not done due to patient refusal. Bold represents five acromegalic patients in disease remission after long-term SSTa suspension (median: 24 months, range: 12–48 months).

Statistical analysis

Data are expressed as mean $\pm$ S.D., unless otherwise stated. IGF-I values were compared with an appropriate age-adjusted range, as reported previously (19), and expressed also as SDS. Nadir GH was defined as the lowest value at any time after OGTT. Data were tested for normality of distribution by Kolmogorov–Smirnov test and log transformed to obtain normal distribution when necessary. Statistical analysis was carried out using paired or unpaired Student's *t*-test, as appropriate. Linear regression analysis was performed to calculate correlation coefficients between different parameters. Values of $P < 0.05$ were considered as statistically significant.

Results

First follow-up (12–16 weeks withdrawal)

At the first evaluation after 12–16 weeks of drug suspension, both serum GH and IGF-I levels significantly increased from 1.0 ± 0.7 to 2.0 ± 1.3 µg/l ($P < 0.001$)

and from 24 ± 8 to 45 ± 31 nmol/l (SDS: from -0.04 ± 1.1 to $+2.8 \pm 3.9$, $P < 0.001$) respectively (Fig. 1). Serum IGF-I concentrations recorded during SSTa positively correlated with those found at the first visit after SSTa discontinuation ($P < 0.05$, $r = 0.44$). Mean fourth finger size of left hand did not significantly change after drug suspension (data not shown). Similarly, all the evaluated metabolic parameters did not vary significantly, except for fasting glucose and HbA1c which significantly decreased in all patients, but in particular those with altered glucose metabolism during SSTa (from 6.7 ± 1.3 to 5.7 ± 1.1 mmol/l, $P < 0.001$ and from 6.2 ± 0.9 to $6.1 \pm 0.6\%$, $P < 0.01$ respectively). Moreover, seven patients with impaired glucose tolerance during SSTa became normally tolerant after drug discontinuation.

When evaluating single patients, 15 showed a rapid disease relapse at the first visit. In particular, seven patients clearly had biochemically active disease, while the other eight showed discrepancies between different parameters (post-glucose GH nadir < 1 µg/l but high IGF-I levels or normal IGF-I levels but GH nadir > 1 µg/l). Seven of these patients also reported a variable

Figure 1 Mean serum GH and IGF-I concentration evaluated as standard deviation scores (SDS) before starting somatostatin analogues (pre-SSTa) during chronic long acting somatostatin analogues therapy (SSTa) and at the first visit after short term drug withdrawal (after 12–16 weeks) in all 27 acromegalic patients.

occurrence of acromegaly-related symptoms and signs (in particular arthralgia and soft tissue swelling). According to the study protocol, these 15 patients restarted SSTa therapy. The remaining 12 patients (1 male and 11 females, 44% of total) were considered to be in biochemical and clinical remission, showing the concomitant presence of all the three current criteria for cure (14) and absence of acromegaly-related symptoms and signs. Out of these 12 patients, 2 are still at 3 months suspension and are currently continuing withdrawal (patient no.s 20 and 23), while the remaining 10 have already been investigated after 6 months of SSTa suspension.

Second follow-up (24 weeks withdrawal)

Only one of the ten patients evaluated after 24 weeks withdrawal showed a biochemical disease recurrence

with elevated basal GH levels despite still normal IGF-I concentrations and restarted SSTa therapy (patient no. 24). The remaining nine patients (33% of total) were found to still be in biochemical and clinical remission (patient no.s 1, 5, 9, 10, 17, 18, 25, 26, and 27). These patients showed lower IGF-I levels recorded during SSTa treatment in comparison to the group of 16 patients with disease relapsing at first or second control visit (-0.8 ± 0.6 vs $+0.4 \pm 1.1$, $P < 0.05$; data not shown). As far as the neuroradiological imaging is concerned, one female previously operated patient showed a slight reduction of the residual tumor mass, while the other eight patients had a stable MRI panel. Subsequently, all of them further continued the follow-up.

Long-term follow-up (over 12 months withdrawal)

Out of the nine patients in remission after 6 months of SSTa withdrawal, five have already exceeded the follow-up from drug discontinuation by over 12 months (1 male and 4 females, 18.5% of total, patient no.s 1, 5, 9, 10, and 17). In particular, one patient reached 18 months, three patients 24 months and one patient 48 months for a total median follow-up period of 24 months. All of them showed relatively stable hormonal levels and absence of clinical/neuroradiological disease recurrence and are currently continuing drug suspension. The trend of serum IGF-I data recorded in these patients during monitoring is described in Fig. 2.

All the historical, hormonal, and neuroradiological characteristics of these five patients in remission after long-term withdrawal are reported in Table 1. In particular, no differences in terms of age, previous treatments, type and duration of SSTa therapy, GH and IGF-I levels before SSTa treatment, fasting GH, and

Figure 2 Serum IGF-I concentrations evaluated as standard deviation scores (SDS), recorded during somatostatin analogues therapy and at each visit after drug withdrawal in the 5 acromegalic patients considered in remission (normal IGF-I concentrations and nadir GH $< 1 \mu\text{g/l}$ (14)) at the long-term follow-up (over at least 12 months of drug withdrawal).

post-glucose GH nadir after drug suspension were observed in respect to other patients.

At the last visit, in these five patients (three affected by DM, one by IGT, and one euglycemic), fasting glucose levels continued to be observed as significantly lower compared to those observed during SSTa (5.8 ± 1.5 vs 7.8 ± 1.4 mmol/l, $P < 0.005$), while HbA1c levels remained only slightly lower (6.3 ± 0.9 vs $6.9 \pm 1.1\%$, $P = \text{NS}$), despite steady BMI levels and the same antidiabetic therapy (two following dietetic regimen and one on insulin plus metformin). All the other evaluated metabolic parameters remained substantially stable during follow-up. Fourth finger size of left hand did not significantly change over the time. As far as MRI was concerned, one *de novo* patient showed the progressive occurrence of an intratumoral imaging compatible with a hemorrhagic area (patient no. 17), while none of the remaining patients developed any visible change of pituitary tumor or residual tumor mass during the long-term drug suspension.

Discussion

This preliminary study demonstrates that chronic treatment with long-acting SSTa may be able to induce a long-term disease remission at least in a subgroup of patients with acromegaly highly sensitive to SSTa therapy. In fact, a long-term persistent biochemical disease control after SSTa withdrawal (over 12 months) was achieved in about 20% of the 27 patients selected according to the presence of constantly 'safe' GH levels, normal IGF-I concentrations, and stable neuroradiological imaging during treatment. This hormonal remission was also accompanied by a persistent clinical well-being and an unchanged tumor/residual tumor volume, challenging the held notion that pharmacological therapy is always a permanent necessity. Moreover, a higher percentage of patients (about 40%) showed at least a short-term biochemical and clinical disease control after drug discontinuation. This last finding also suggests the possibility of a scheduled periodical 3–6 month duration SSTa suspension without inducing any hormonal deterioration.

The mechanisms responsible for the long-term control of hormone secretion and tumor growth induced by SSTa therapy are at present unknown. However, SST has been shown to be a powerful inhibitor of neovascularization, by acting directly on endothelial cells or indirectly on the production of angiogenic growth factors (20). Furthermore, previous studies indicated that somatostatin and its analogs exert antiproliferative effects with cytostatic (growth arrest) and cytotoxic (apoptosis) consequences (21, 22). Consistent with these data, it is tempting to speculate that the long-term remission observed in a subset of patients might be due to the antiangiogenic and antiproliferative actions of SSTa,

although further basic research is required to clearly understand this phenomenon.

Some previous studies conducted in small groups of patients demonstrated the possibility of prolonging intervals between o-LAR injection to every 6–8 weeks without reduction in efficacy (23, 24). In addition, at least two further papers evaluated the duration of o-LAR or l-SR suspension required to obtain a correct washout, fixing it at about 3 months (25, 26). By contrast, only one study specifically investigated a long-term SSTa suspension and reported safe GH and normal IGF-I levels after 5 months withdrawal in one of the seven patients well responsive to 12 months o-LAR therapy (27). The present study first demonstrates the possibility to obtain a long-lasting remission of acromegaly after a long-term SSTa suspension. Moreover, it suggests at least the need for a periodical SSTa discontinuation to evaluate the disease evolution in each patient, particularly in those well controlled by SSTa therapy. In view of programming SSTa discontinuation and follow-up intervals, it is worth noting that recurrence within 3 months from drug suspension was seen in almost all patients, while among those who prolonged the monitoring only one showed disease reappearance after 6 months withdrawal. In fact, in all the other monitored patients, no clear recurrence during the follow-up period (up to 6 months in four patients, 18 months in one, 2 years in three, and 4 years in one) was observed. Admittedly, the number of patients included in this series is still too small and the period of follow-up too short to draw definitive conclusions.

As far as the metabolic parameters were concerned, it is important to consider that glucose homeostasis showed some changes during the suspension period. In fact, glucose metabolism clearly and rapidly improved after short-term withdrawal in all patients, closely mirroring the absence of detrimental insulin inhibition by SSTa. Moreover, even during the long-term reevaluation of patients in biochemical remission, fasting glucose levels remained steadily lower than those recorded during SSTa.

All subjects who resulted in remission after withdrawal appeared to have at least two specific common characteristics. First, a majority of five patients in long-term remission (more than 12 months) were previously operated by unsuccessful neurosurgery except one *de novo* patient (one showing the occurrence of hemorrhagic intratumoral area after 12 months of SSTa withdrawal). This observation is consistent with previous data demonstrating that about 75–80% removal of the tumor by neurosurgery (debulking) improves hormonal control of acromegaly by SSTa (28, 29). Secondly, the patients in median term remission (24 weeks) showed IGF-I concentrations lower than those found in other patients also during SSTa treatment. Thus, this study further confirms that IGF-I is the most important biochemical parameter to monitor during

SSTa therapy, and provides new evidence that it may be considered the main predictive parameter of a long-lasting disease control after drug withdrawal. On the contrary, no other differences in terms of age, previous neurosurgery, duration and type of SSTa therapy, GH and IGF-I levels before SSTa treatment, and GH levels after drug suspension were observed.

In conclusion, chronic SSTa therapy seems to be able to induce a long-term hormonal and clinical disease remission at least in a subgroup of carefully selected patients with acromegaly previously found to be highly sensitive to SSTa therapy. In this respect, IGF-I levels during SSTa treatment seem to be the main predictive parameter of disease control even after drug withdrawal. These data challenge the previously held concept that medical therapy is always a lifelong requirement, even if a close follow-up must be performed over the time and the resumption of treatment must be restarted whenever necessary.

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