Is MRI follow-up relevant in patients with GH-secreting pituitary adenomas primarily treated and responsive to long-acting somatostatin analogues (SMSa)?

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Abstract

Objective: Primary SMSa treatment can be associated with hormonal control and tumor shrinkage in patients with GH-secreting pituitary adenomas. The aim of this study was to evaluate whether regular MRI follow-up was necessary in patients with acromegaly-treated and responsive to first-generation long-acting SMSa.

Patients and methods: In this retrospective monocentric study we included patients with GH/IGF-1 hypersecretion and pituitary adenomas with normal visual field, primarily treated with first-generation long-acting SMSa between 1995 and 2015 and regularly monitored (clinical evaluation, GH/IGF-1 levels and pituitary MRI) for at least 3 years.

Results: We included 83 patients (32 men and 51 women, mean age at diagnosis 50 ± 12 years) with mean GH = 19.3 ± 25.6 ng/mL, IGF-1 = $284 \pm 110\%$ ULN and pituitary adenoma height = 12.9 ± 4.7 mm. Mean follow-up was 8.9 ± 4.9 years in 36 controlled patients and 2.0 ± 1.6 years in 47 partial responders to SMSa alone. No significant increase in pituitary adenoma height was observed. Pituitary adenoma height decreased significantly in controlled patients (diagnosis: 11.9 ± 4.8 mm, SMSa: 9.6 ± 3.3 mm, $P < 0.001$), and in partially responders (diagnosis: 13.6 ± 4.5 mm, SMSa: 11.5 ± 4.5 mm, $P < 0.001$).

Conclusion: During SMSa treatment, no significant increase in GH-secreting adenoma size was observed. Primary SMSa treatment was associated with a significantly decrease in adenoma height in our population. Our cohort data suggest that regular MRI follow-up does not seem relevant in patients with acromegaly who are responsive to SMSa treatment.

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Introduction

Acromegaly, defined as autonomous hypersecretion of GH/IGF-1, is linked to pituitary adenoma in the majority of patients. GH/IGF-1 hypersecretion causes an increase in morbidity and mortality due to the possible metabolic, cardiovascular and neoplastic complications (1). Moreover, adenomatous growth can cause tumor complications, the most frequent of which is optic chiasm compression.

The treatment of patients with acromegaly should normalize hormonal hypersecretion while controlling pituitary tumor growth. First-line treatment consists of pituitary surgery performed by an expert neurosurgeon. Pituitary surgery, particularly in patients with macroadenoma, may be non-curative with incomplete adenomatous resection requiring adjuvant medical treatment and may cause complications including partial

or complete pituitary insufficiency requiring lifelong hormonal supplementation (2, 3).

The presence of somatostatin receptor subtypes on GH-secreting cells is the basis for the use of somatostatin analogues in patients with acromegaly. The long-acting forms of first-generation SMSa (octreotide LAR and lanreotide Autogel) have proven their efficacy, in the short and long term, in controlling both GH/IGF-1 hypersecretion (4, 5, 6) and adenoma size (4, 7, 8). The decrease in adenoma size induced by SMSa is greater when they are prescribed as first-line therapy than as adjuvant therapy after pituitary surgery (9). Therefore, first-generation SMSa, which are widely used in postoperative care, are also indicated for primary treatment in some patients with acromegaly and are even recommended in cases of invasive adenoma that cannot be cured by surgery, and when there are contraindications or refusal of surgical management (10, 11).

The modalities for monitoring the size of pituitary adenoma by MRI of the sellar region were not described in the latest international (11) and Endocrine Society (12) consensus for patients with acromegaly eligible for first-line treatment with first-generation SMSa.

The objectives of this clinical study were to evaluate variations in adenoma height in patients with GH-secreting adenoma during primary and prolonged treatment with first generation SMSa and to question the value of regular MRI monitoring in these patients.

Patients and methods

In this descriptive and retrospective study, patients were included for whom a diagnosis of acromegaly (increased IGF-1, lack of GH suppression during OGTT) related to pituitary adenoma was made between 1995 and 2015. Patients had first-line treatment with first-generation SMSa (lanreotide Autogel, octreotide LAR) alone. Concerning GH-secreting macro-adenoma, patients with extension into the cavernous sinus and/or high GH/IGF-1 levels were primarily treated with SMSa. Other patients have been included in an international clinical study in order to evaluate the tumoral response to primary medical treatment with lanreotide autogel 120 mg every 4 weeks (13). Finally patients with contraindications to surgery were treated with SMSa as primary treatment. For micro-adenomas the main indication of primary treatment with somatostatin analog was patient's refusal of surgery, and rarely contact of the GH-secreting microadenoma with the homolateral sinus cavernous. Patients also had regular

clinical, hormonal and neuro-radiological monitoring with an annual IGF-1 and GH assay and pituitary MRI every 12–18 months, for at least 3 years.

Patients with a diagnosis of mixed-cell adenoma based on biological data (GH hypersecretion associated with PRL >100 ng/mL, co-secretion of ACTH, TSH-dependent hyperthyroidism), a visual field defect or a normal pituitary MRI on diagnosis were excluded.

Patient data were collected through computerized records or paper archives until a change in treatment, if any. During follow-up, these therapeutic modifications could consist of an optimization of medical treatment (association of SMSa with dopamine agonist (DA) or pegvisomant, replacement of the SMSa by pegvisomant), or even pituitary surgery, possibly supplemented by radiotherapy.

Clinical data on signs secondary to hormonal hypersecretion or a possible tumor syndrome (headache, visual field abnormalities) were collected during patient follow-up. Concentrations of IGF-1 and GH were collected at diagnosis and then at each clinical assessment. GH/IGF-1 hypersecretion was considered to be control when IGF-1 remained within the normal range for age and gender and GH was less than 2.5 ng/mL during follow-up. A patient was considered to be resistant to SMSa therapy if the concentration of IGF-1 did not decrease by more than 10% after treatment at a maximum dose for 3–6 months. The other patients were uncontrolled (or partial responders). Data for the exploration of the other pituitary axes (corticotrophic, thyrotrophic and gonadotrophic) were collected during diagnosis and treatment follow-up to assess the presence or appearance of partial or complete anterior pituitary insufficiency.

Plasma GH and IGF-1 determinations were performed using standard techniques at the Biochemistry Laboratory of our University Hospital and were most often measured within 24–48 h before SMSa injections in treated patients.

Image analysis

MRI scans were reviewed by the same radiologist who was blinded to history and clinical data. To compare the MRI images, the height of pituitary adenomas was measured along the coronal plane, perpendicularly to the optic chiasm, where the adenoma was most visible (usually T2-weighted images or post-gadolinium T1-weighted images). The optic chiasm was chosen as the reference because the major complication that would motivate a therapeutic modification is optic chiasm compression. For controlled patients, the MRI images at diagnosis and the

last MRI scan available were reviewed and compared. With regard to uncontrolled patients who needed a treatment change, the first MRI scan was compared to the last available scan before treatment modification. When an alternating decrease/increase in adenoma size was mentioned in the routine follow-up, all MRI images were reviewed and compared for the study. Arbitrarily and by reference to clinical practice, for this study any difference in height of 2 mm or more was considered as clinically significant.

Statistical analysis

The statistics were performed with the Stata software®. Descriptions were based on averages and s.d. The qualitative variables were compared by a chi-square test when the theoretical numbers were greater than 5 or by a Fisher's test. The quantitative variables were compared by a Student *t*-test when the conditions of use were met or by a Mann-Whitney test. Correlations were performed by a non-parametric Spearman test. A test was considered significant for $P < 0.05$.

This work conforms to the Declaration of Helsinki, Good Clinical practice Guideline. All patients have been informed and gave signed consent for clinical, hormonal and radiological analysis of their data after explanation of the purpose of the study.

Results

Description of the population

One hundred seventy-six patients with acromegaly were seen in the endocrinology department between 1995 and 2015. Ninety-three patients were excluded: 46 patients did not receive first-line treatment with SMSa, 35 were treated surgically, 9 received dopamine agonist therapy and 2 received pituitary radiotherapy. A visual field alteration was present at diagnosis in eight patients and for five patients no adenoma was noted on the initial MRI. A mixed-cell adenoma was found in 14 patients. A lack of initial data or lack of follow-up imaging data resulted in the exclusion of 18 patients. One patient had an initial stroke and another had acromegaly associated with GHRH secretion (Fig. 1).

Therefore, 83 patients with GH/IGF-1 hypersecretion related to pituitary adenoma received first-line treatment with the long-acting forms of SMSa and were followed for at least 3 years. 36 (43%) patients had hormonal control (IGF-1 normal for age and sex and GH

< 2.5 ng/mL) during treatment with SMSa until the end of follow-up (controlled group). 47 (57%) patients were not hormonally controlled by SMSa alone and required treatment adjustments (uncontrolled group). In this group, 12 patients were treated with SMSa alone for at least 3 years and 35 patients had a treatment modification before 3 years. 34 of these 47 patients were treated secondarily with a combination of SMSa and dopamine agonists. Seven patients were treated with pegvisomant alone or in combination with SMSa. Finally, 21 patients were surgically managed. Among these patients, 4 had a decrease in IGF-1 of $< 10\%$ 3–6 months after the first injections of the analog and were considered resistant: 1 of these patients had second-line surgery, 3 were treated with a SMSa/dopamine agonists combination, and this was before surgery for 2 of these patients.

Two patients (2.4%) had MEN 1 mutations and were hormonally controlled. One patient (1.2%) had McCune Albright syndrome and would be treated with a SMSa alone for less than 3 years before being treated with the SMSa/dopamine agonist combination.

Figure 1
Flow chart.

Clinical Study	N Grandgeorge and others	MRI follow-up in acromegaly	182:1	126
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Table 1 Characteristics of the population at diagnosis. The calculation of *P* is based on the comparison between controlled and uncontrolled groups. The data are expressed as an average ($\pm$ s.d.).

	Total Pop (<i>n</i> = 83)	Controlled (<i>n</i> = 36)	Uncontrolled (<i>n</i> = 47)	<i>P</i>
Age at diagnosis (years)	50.1 $\pm$ 12.1	54.4 $\pm$ 10.6	46.8 $\pm$ 12.3	0.004
Women (<i>n</i> (%))	51 (61.5)	26 (72.2)	25 (53.2)	0.06
Follow-up period (years)	5.0 $\pm$ 4.8	8.9 $\pm$ 4.9	2.0 $\pm$ 1.6	<0.0001
IGF1 at diagnosis (ULN)	283.7 $\pm$ 110.2 (<i>n</i> = 79)	266.2 $\pm$ 129.9 (<i>n</i> = 34)	297 $\pm$ 91.9 (<i>n</i> = 45)	0.03
GH at diagnosis (ng/mL)	19.3 $\pm$ 25.6 (<i>n</i> = 77)	12.5 $\pm$ 16.5 (<i>n</i> = 32)	24.1 $\pm$ 29.7 (<i>n</i> = 45)	0.03
Diameter of the adenoma at diagnosis (mm)	12.9 $\pm$ 4.7	11.9 $\pm$ 4.8	13.6 $\pm$ 4.5	0.03

Characteristics of the population at diagnosis

The 83 patients included were treated with first-generation SMSa for 5.0 $\pm$ 4.8 years. Sixteen patients (19.2%) had monthly i.m. injections of LAR octreotide and 67 patients (80.7%) were treated with lanreotide Autogel, one s.c. injection every 4 weeks. The main characteristics of the population are summarized in Table 1. These were 51 women (61.5%) and 32 men, with an average age of 50.1 $\pm$ 12.1 years with pituitary adenoma (macro >10 mm = 65 (78.3%), micro <10 mm = 18 (21.7%)) responsible for growth hormone hypersecretion (mean GH 19.3 $\pm$ 25.6 ng/mL, IGF-1 ULN 283 $\pm$ 110%).

Comparison of the controlled and uncontrolled groups

There was an insignificant trend toward poorer hormonal control in men than in women (*P* = 0.06). Patients controlled by SMSa were older (*P* = 0.004).

Concentrations of IGF-1 and GH at diagnosis were statistically higher in uncontrolled patients than in controlled patients, respectively IGF-1 = 297 $\pm$ 92 vs 266 $\pm$ 130% ULN (*P* = 0.03); GH = 24.1 $\pm$ 29.7 vs 12.5 $\pm$ 16.5 ng/mL (*P* = 0.03).

The height of the adenoma was greater in uncontrolled patients (13.6 $\pm$ 4.5 mm) than in controlled patients (11.9 $\pm$ 4.8 mm, *P* = 0.03).

Hormonal change during treatment with SMSa

During primary treatment with SMSa in all 83 patients, a decrease in IGF-1 and GH concentrations was observed. This was statistically more significant in controlled subjects (Table 2).

Hormonal control (normal IGF-1 for age and sex, GH <2.5 ng/mL) was obtained in 36 (43%) patients and 47 (57%) patients had a decrease in GH/IGF-1 without being normalized (uncontrolled).

With regard to anterior pituitary function, there were no significant differences in terms of presence at diagnosis or appearance during follow-up of anterior pituitary insufficiency (thyroid, gonadotropic, corticotropic) between controlled and uncontrolled patients.

Change in adenoma height during treatment with SMSa

On average, controlled patients had 6.5 MRI scans over the course of follow-up of 8.9 $\pm$ 4.9 years, while uncontrolled patients had 2.4 MRI scans over a period of 2.0 $\pm$ 1.6 years of treatment with SMSa alone.

In the 83 patients treated with somatostatin analogues, no significant increase (>2 mm) in adenoma height was noted on MRI monitoring, regardless of whether primary treatment with SMSa normalized GH/IGF-1 hypersecretion.

Table 2 Hormonal and tumor changes during SMSa treatment. The calculation of *P* is based on the comparison of controlled vs uncontrolled groups. The data are expressed as an average (s.d.).

	Total Pop (<i>n</i> = 83)	Controlled (<i>n</i> = 36)	Uncontrolled (<i>n</i> = 47)	<i>P</i>
IGF1 decrease in 3–6 months (%)	48.6 $\pm$ 25.3 (<i>n</i> = 78)	63.8 $\pm$ 19.1 (<i>n</i> = 34)	37 $\pm$ 23.5 (<i>n</i> = 44)	<0.0001
IGF1 last evaluation (ULN)	147.4 $\pm$ 84.7	76 $\pm$ 25.6	202.1 $\pm$ 72.3	<0.0001
GH last evaluation (ng/mL)	3.1 $\pm$ 3.4 (<i>n</i> = 77)	1.2 $\pm$ 0.8	4.8 $\pm$ 3.9 (<i>n</i> = 41)	<0.0001
Height of adenoma last evaluated (mm)	10.7 $\pm$ 4.1	9.6 $\pm$ 3.3	11.5 $\pm$ 4.5	0.02
Decrease in adenoma height (mm)	2.2 $\pm$ 3	2.4 $\pm$ 3.5	2.1 $\pm$ 2.6	0.9

Thirty-three patients had a decrease in adenoma height (39.7%) and 50 had a stable adenoma during follow-up (60.2%). A decrease in adenoma height was observed in the controlled and uncontrolled groups with heights ranging from 11.9 ± 4.8 mm to 9.6 ± 3.3 mm ($P=0.01$) and 13.6 ± 4.5 mm to 11.5 ± 4.5 mm ($P=0.02$) respectively (Fig. 2). There was no significant difference in the decrease in adenoma height between these two groups, which was 2.4 ± 3.5 mm vs 2.1 ± 2.6 mm ($P=0.9$) respectively in the controlled and uncontrolled group. On the other hand, there was a significant correlation between the decrease in adenoma height during treatment and adenoma height at diagnosis ($r=0.49$, $P=0.0002$) (Fig. 3). It should be noted that in a single patient with a hormonal control and GH-secreting microadenoma, MRI monitoring showed an initial decrease in adenoma height (from 9 to 5 mm) with a secondary increase in adenoma height (5–8 mm) due to clinically asymptomatic hemorrhagic transformation. Comparison of the initial MRI and the last MRI scans revealed no significant variation in the height of this adenoma during SMSa treatment (variation of 9–8 mm).

Discussion

Primary and prolonged treatment with first-generation SMSa in 83 patients resulted in control of GH/IGF-1 hypersecretion in more than 40% of the patients with an average decrease in pituitary adenoma height of more than 2 mm. In addition, in patients who responded hormonally to SMSa therapy, there was no significant increase in adenoma height during extended MRI monitoring.

While endoscopic adenomectomy is the first-line treatment for patients with pituitary microadenoma or intra-sellar adenoma, the presence of somatostatin receptor subtypes on GH-secreting cells means that SMSa have anti-secretory and anti-tumor effects in some patients with acromegaly. Recent studies show that a response is observed in 25–45% of patients (11, 14).

In our study, primary treatment with first-generation SMSa resulted in control of GH/IGF-1 hypersecretion (IGF-1 normal for age and sex, GH <2.5 ng/mL) in 36/83 patients (43%) during treatment for 8.9 ± 4.9 years. In the Primary study (13), primary treatment with lanreotide Autogel 120 mg/month for 1 year in patients with GH-secreting macroadenoma resulted in hormonal control in 34.1% of the patients, a difference that may be secondary to the different therapeutic protocols, the patients studied or essentially to the duration of medical treatment, with hormonal control increasing over the duration of the

Figure 2

Change in IGF-1 (A), GH (B), adenoma height (C) during treatment with somatostatin analogues. Comparison of IGF-1, GH and adenoma height before and after treatment with somatostatin analogues in the total population, controlled and hormonally uncontrolled by somatostatin analogues. The data are expressed as an average $\pm$ S.D. * $P < 0.05$; ** $P < 0.01$.

Figure 3

Correlation between the initial height of the adenoma and the decrease in the adenoma height during treatment with somatostatin analogues. $r = 0.49$; $P < 0.0002$

treatment (5). Control of GH/IGF-1 hypersecretion was more frequent in the elderly ($P < 0.004$), when the IGF-1 at diagnosis was lower ($P = 0.03$) and was better in women ($P = 0.06$) as reported in the literature (15, 16, 17).

Although there is no correlation between hormonal response and anti-tumor effect, first generation SMSa (octreotide LAR, lanreotide Autogel) may also induce a decrease in GH-secreting adenoma volume, and the anti-tumor effect is greater during primary treatment than after pituitary surgery, radiotherapy or other medical treatment (18, 19). In the Guistina meta-analysis, a significant decrease in adenoma volume was observed in 53% (45–61%) of the patients with acromegaly treated with octreotide (18). Mazziotti G *et al.* also reported a variable decrease (10–71%) in adenoma volume in 32.7% of patients treated with lanreotide SR or lanreotide Autogel, and a decrease in adenoma volume was more frequent in patients with macroadenoma (19). In our study there was a positive correlation ($P < 0.001$) between the decrease in adenoma height during treatment with SMSa and the initial height of the GH-secreting adenoma. Finally, in the Primarys study (13), monthly treatment with lanreotide Autogel 120 mg resulted in a significant decrease in the volume of GH-secreting macroadenomas as early as the 3rd month, predicting the hormonal response at 48 weeks (20), and an increase in adenoma volume was observed in 9 of the 89 patients evaluated, and by more than 20% in 2 of them. The literature shows very extensive heterogeneity in the decrease in adenoma volume observed in 20–80% of patients treated with SMSa. This heterogeneity is not explained solely by the linear or volumetric method of assessing adenoma size (18, 19). In our study, we used a

linear method, one that is validated, simple and possible to use in daily practice to evaluate a significant change in the size of a pituitary adenoma (11). There was an average decrease in adenoma height in patients who responded to SMSa treatment, whether they were controlled or uncontrolled. But most importantly, no patient experienced clinical pituitary tumor syndrome or a significant and persistent increase in adenoma height during follow-up. It should be noted that the only increase in adenoma height (3 mm) after an initial decrease was secondary to a clinically asymptomatic hemorrhagic transformation of microadenoma. In a study of MRI monitoring of macroprolactinomas controlled by medical treatment with dopamine agonists, tumor shrinkage was observed in most patients and 18% had an increase in adenoma volume secondary to asymptomatic hemorrhagic transformations (21). Therefore, in patients with acromegaly sensitive to SMSa, the effects on tumor volume reduction are less significant than those observed during treatment with dopaminergic agonists in prolactinoma. All of these data suggest the value of an early MRI examination (3–6 months), along with hormonal evaluation to eliminate the rare patients resistant to medical treatment with SMSa and to predict whether the patient will be sensitive to treatment with SMSa. However, the appearance of clinical signs suggestive of pituitary apoplexy during this medical treatment calls for a pituitary MRI.

This study involved a large cohort of patients who received primary treatment with first-generation SMSa, including not only hormonally controlled patients treated over the long term with SMSa, but also hormonally uncontrolled patients who required therapeutic intensification. No therapeutic intensification was justified in patients with insufficient hormone control due to an increase in adenoma volume.

The retrospective nature of our study is its main limitation. However, the MRI review was performed by a single neuro-radiologist, blinded to the patient's clinical history, and all patients treated with first-line SMSa were included, regardless of hormonal control during a follow-up of at least 3 years.

Finally, the place of first-generation SMSa in the treatment of patients with acromegaly seems more important in recent guidelines (11). However, the modalities of neuro-radiological monitoring by pituitary MRI during medical treatment with SMSa is not well specified, particularly during primary treatment (12). Pituitary MRI is recommended for diagnosis in all patients with secreting or non-secreting pituitary adenoma, but the frequency of follow-up MRIs during medical

treatment varies according to the type of adenoma and the patient's treatment. The results of this study could modify the neuro-radiological monitoring of patients with acromegaly by decreasing the frequency of pituitary MRIs during primary and prolonged treatment with SMSa.

Declaration of interest

P C is on the editorial board of *EJE*. P C was not involved in the review or editorial process for this paper, on which he is listed as an author. The other authors have nothing to disclose.

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Author contribution statement

N G was involved in patients enrollment into the study, analysis and interpretation of the data; and drafting of the manuscript. G B was involved in neuro-radiology study and review MRI scans of all patients. S G was involved in patient enrollment into the study, analysis and interpretation of the data; P C and F B were involved in concept and design of the study; patient enrollment into the study; analysis and interpretation of the data. All authors additionally revised the work critically for important intellectual content, approved the final version to be published, and agree to be accountable for all aspects of the study.

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