Research paper

Beneficial effect of dose escalation and surgical debulking in patients with acromegaly treated with somatostatin analogs in a Romanian tertiary care center

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ABSTRACT

BACKGROUND: Somatostatin analogs (SSA) are now considered standard therapy for acromegaly, as primary or adjunctive treatment after pituitary surgery. OBJECTIVE: To evaluate the efficacy of SSA and the effect of dose escalation in non-operated patients with acromegaly as compared to patients treated after pituitary surgery in a Romanian tertiary care center. DESIGN: Retrospective study of 73 consecutively evaluated patients with acromegaly treated with SSA, divided into 2 groups: 11 patients (4M/7F, 21-62 years) with primary treatment and 62 patients (22M/40F, 21-68 years) treated after surgery. They received Octreotide LAR 20–30 mg i.m./28 days or Lanreotide SR 30 mg i.m./14/10/7 days. Random serum growth hormone (GH) was measured using IRMA, sensitivity 0.2-0.01 μg/L IGF-1 was measured using different assays and compared with ULN for age and sex. RESULTS: Overall, random GH ≤2.5 μg/L was attained in 39 patients (53.4%) and optimal GH ≤1 ng/mL) in 30 patients (41%), while normal IGF-1 was recorded in 22/72 patients (30.5%). The final random GH ≤2.5 μg/L was achieved in 27.2% of non-operated patients (3/11) as compared with 58% (36/62) of patients treated medically after pituitary surgery, p<0.05. Escalation of doses of SSA applied in 43 patients improved the number of controlled patients by 5 (12.1%, p=0.059) and the number of optimally controlled patients by 9.7%. Of the 8 patients who switched from Lanreotide to Octreotide, 2 patients achieved GH normalization. CONCLUSION: The rate of biochemical control via SSA treatment in patients with acromegaly could be improved by rise of the SSA dose or by debulking surgery. Occasionally, substituting one SSA for another may be of benefit.

Key words: Acromegaly, Dose escalation, Pituitary surgery, Somatostatin analogs

INTRODUCTION

Acromegaly is a rare disease usually caused by a GH-secreting pituitary adenoma producing excess growth hormone (GH) and insulin-like growth factor 1 (IGF-1). Uncontrolled acromegaly is associated with a two- to threefold increase in mortality compared with age- and sex-matched healthy controls.[1-3] Death is due predominantly to cardio-cerebrovascular disease, respiratory disease and, in some studies, to malignancy.[3] Controlling GH and IGF-1 hypersecretion is the primary goal of treatment in order to lower mortality rates. Earlier studies have indicated that random GH <2.5 µg/L (measured by radioimmunoassays) and normal serum IGF-1 are both correlated with a standardized mortality ratio close to that of the general population,[2] the effect of GH normalization being more extensively reported in the literature.[3]

Recent consensus guidelines recommend more stringent values for 'cure' or control of acromegaly, i.e. random GH levels below 1 µg/L or OGTT nadir GH <1 µg/L or even <0.4 µg/L (if measured by ultrasensitive immunoassays) and normal age-related IGF-1 levels.[4,5] Treatment of acromegaly frequently requires a multimodality approach to control disease progression. Besides pituitary surgery, with better results being achieved in dedicated neurosurgical centers,[6] somatostatin receptor ligands (somatostatin analogs, SSA) are now considered standard therapy for acromegaly, either as primary or adjunctive treatment. They suppress GH secretion by the pituitary and GH-secreting adenomas, decrease binding to hepatocyte GH receptors, inhibit hepatic IGF-1 synthesis and control tumor growth.[7] Clinical studies with the most extensively used depot SSA, Octreotide LAR (OCT) and Lanreotide slow-release (LAN) have shown variable results.[8] Conventional doses of Octreotide LAR (20–30 mg/month) induced biochemical control (GH levels <2.5 µg/L) between 42% and 72% and IGF-1 normalization in 38–67% of patients, respectively,[9–11] while Lanreotide slow release (SR) reduced plasma GH levels in 49–54% of patients and normalized IGF-1 levels in 51–59% of patients.[12,13] Clinically significant tumor shrinkage has been reported in 66% of patients treated with OCT-LAN[14] and in 32% of patients treated with LAN-SR or Autogel.[15] Escalation of the SSA doses has been shown to improve biochemical control in patients resistant to conventional doses[9,10,13] while demonstrating a similar tolerability profile.[16]

We analyzed retrospectively, in an unselected population of Romanian patients with acromegaly assessed in a single center, the efficacy of SSA treatment and the effect of progressive increase of SSA doses in patients not surgically treated as compared to patients treated with SSA after pituitary surgery.

PATIENTS AND METHODS

We evaluated 73 patients with acromegaly treated with SSA, admitted to the Department of Neuroendocrinology between 2007 and 2012. Patients with acromegaly and hyperprolactinemia treated with stable doses of dopamine-agonist were not excluded. The diagnosis of acromegaly was defined in all patients by high serum GH levels not suppressible <1 µg/L after 75 g–2 h glucose load (OGTT) and high plasma IGF-1 levels for age.

Patients were divided into 2 groups

Group A included 11 patients with pre-surgery treatment with SSA: 4 men, 7 women, median age at diagnosis 42.0 years (range 21–62 years); one of these patients had had previous pituitary radiotherapy (high-voltage radiotherapy) 19 years before the SSA treatment and linear accelerator gamma-knife radiotherapy 7 months before the SSA treatment. Based on pituitary imaging, 10 patients had a macroadenoma, 1 patient had a microadenoma and in 5 patients the tumors had signs of invasion into the surrounding structures.

Group B included 62 patients who received treatment with SSA after pituitary surgery. Forty-one of these patients had also had previous radiotherapy. There were 22 men and 40 women, median age at diagnosis 40.50 years (range 21–68 years). Before surgery, 57 patients had a macroadenoma (in 21 patients with signs of invasion into the surrounding structures), 4 patients had a microadenoma, while in 1 patient the initial tumor volume is unknown. At initiation of the SSA treatment, 35 patients had pituitary remnants ≥1 cm, 27 patients <1 cm.

All patients signed an informed consent form to approve diagnostic testing, treatment decision,

methods for follow-up and treatment of the data for scientific purposes.

Treatment

In Romania, treatment with SSA is supported by the National Health Insurance House for patients with active acromegaly after pituitary surgery ± radiotherapy or as primary therapy only for patients with macroadenomas >2 cm in diameter or with clear signs of tumor invasion into the surrounding tissues. The patients were not selected for therapy based on their response to an acute test to Octreotide 0.1 mg s.c.

The somatostatin analogs used were Octreotide – long-acting release (OCT- LAR) at doses of 20 – 30 mg i.m. at 28-day intervals or Lanreotide – slow release (LAN – SR) at doses of 30 mg i.m. at 14, 10 or 7-day intervals. In all but 2 patients, the treatment was started with the lowest dose and was increased in patients who did not normalize GH and/or IGF-1, this determined after assessment of the response at 3-6 months. In 43 patients the response to treatment was assessed both on the low (OCT 20 mg i.m./28 days or LAN 30 mg i.m./14 days) and the higher dose (OCT 30 mg i.m./28 days or LAN 30 mg i.m./10 or 7 days). Thirty-seven patients had been initially treated with LAN-SR, 36 patients with OCT-LAR. Nine patients received both drugs consecutively and the responses to each treatment were compared.

Criteria for disease control

The patients were considered controlled if fasting GH levels were ≤2.5 μg/L in the presence of normal IGF-1 levels for sex and age. The subgroup of patients having at least one GH level ≤1 μg/L (either fasting or after 75g-OGTT) in the presence of normal IGF-1 levels for sex and age was considered optimally controlled, as recommended by the latest diagnosis guidelines for acromegaly.[4] During the study period, GH levels were determined in our center by different immunoradiometric assays. The assays sensitivity ranged accordingly (from 0.2 to 0.01 μg/L). Random GH levels were measured either as a mean of a GH daily curve (4 samplings at 4 hours interval) or in the baseline blood sample from 75 g-OGTT.

Serum IGF-1 was measured by different commercial assays in different laboratories. IGF-1 data are shown as measured serum values and as the ratio with the upper limit of the normal range for sex and age in each assay (ULN; normal ≤1).

SSA treatment side-effects

Data were retrieved from the medical files of the patients.

Tumor evaluation

Tumor size was measured in the majority of patients via computed tomography (CT) or via magnetic resonance imaging (MRI) studies. The images were reviewed by two experienced radiologists (D.H and A.D.). We calculated the tumor area using the ellipsoid formula (coronal vertical × transversal diameter × π/4). A reduction of at least 25% of the tumor area after treatment was considered significant.

Statistical analyses

The data were analyzed using SPSS software (version 11.0; SPSS Inc., Chicago, IL) and are reported as mean ± standard deviation for variables with normal distribution or as median [range] in the case of deviations from normality. The ANOVA model and 2-tailed Student's t-test were used to compare the variables with a normally distributed value; the Mann-Whitney test was used for the parameters with skewed distribution. Spearman's coefficients with a 95% confidence interval were calculated for correlations. Multivariate regression analysis then identified independent predictive parameters. The comparison between baseline and the final data was performed by the Wilcoxon matched pair test. The χ^2 test was used for categorical variables. $P < 0.05$ was considered statistically significant.

RESULTS

The characteristics of the patients and their tumors before treatment with somatostatin analogs are summarized in Table 1.

SSA efficacy on GH and IGF-1 secretion

The patients were evaluated before and during treatment with SSA for a period of 16 ± 10.5 months (range 3–44 months). At the final evaluation, 45 patients (62%) were on high-dose SSA. SSA treatment induced a significant decrease of random serum GH (median) from 7.8 μg/L [1.2–176] to 2.3 μg/L [0.1–71.1], p <0.001, and of serum IGF-1 (median) from 2.48 ×

Table 1. Baseline characteristics of patients with acromegaly treated with somatostatin analogs (SSA)

	SSA before surgery N = 11	SSA after surgery N = 62	p
Age at diagnosis (median, range) (years)	42.00 [21 – 62]	40.50 [21 – 68]	NS
Sex	4 M : 7 F	22 M : 40 F	NS
Previous radiotherapy, n (%)	1 (9.09)	41 (66.12)	0.001
SSA treatment duration (median, range) (months)	9.00 [3 – 17]	15.00 [3 – 44]	0.007
Tumor size at diagnosis (n)	10 macro, 1 micro (<1 cm)	57 macro, 4 micro, 1 unknown	NS
Tumor size before SSA (n)	9 macro, 2 micro	42 macro, 20 micro	NS
Tumor area at diagnosis (median, range) (cm^2)	3.41 [0.51-9.97] (n = 9)	1.89 [0.5-13.06] (n = 58)	NS
Tumor area before SSA(median, range) (cm^2)	3.43 [0.51-9.97]	0.64 [0.5-9.80]	<0.05
Invasive tumor, n (%)	5 (45.4)	21 (33.8)	NS
Random serum GH before SSA (median, range) (µg/L)	25.10 [4.35-176]	6.80 [1.2-162]	0.09
Serum IGF-1 before SSA, × ULN (median, range)	3.56 [2.30-7.40]	2.20 [0.5-9.40]	<0.05
Treatment	LAN-SR: 1 OCT-LAR: 10	LAN-SR: 36 OCT-LAR: 26 Both consecutively: 9	

Legend: ULN = IGF-1 upper limit of normal range for age, macro -macroadenoma, micro -microadenoma

ULN [0.5–9.4] to 1.46 × ULN [0.49–4.8], p <0.001.

Overall, random GH ≤2.5 µg/L was recorded at the last evaluation in 39 patients (53%) and optimal GH (any random or OGTT GH ≤1 µg/L) in 30 patients (41%), while normal IGF-1 was recorded in 22 patients (31%). Both GH ≤2.5 µg/L and normal IGF-1 were recorded in 18 patients (25%) and optimal GH and normal IGF-1 in 19 patients (26%).

The pre-treatment tumor area and random serum GH levels before treatment were independently pre-dictive for post-treatment GH levels (coeff. B=2.58, 95% CI [1.22–3.93], p <0.001, and coeff. B=0.23, 95% CI [0.14–0.31], p <0.001, respectively).

SSA efficacy in patients treated before or after pituitary surgery

The comparison between operated and non-operated patients treated with SSA therapy is shown in Table 1 (baseline characteristics before treatment), Table 2 (efficacy of the treatment) and Figure 1.

Table 2. Results of the treatment with somatostatin analogs before or after pituitary surgery in patients with acromegaly

	SSA before surgery N = 11	SSA after surgery N = 62	p
Random serum GH µg/L, median [range]	12.10 [0.46 – 71.1]	2.0 [0.1 – 64.0]	<0.05
Serum IGF-1 × ULN, median [range]	2.30 [1.5 – 4.8]	0.49 [0.4 – 4.1]	<0.001
Random serum GH ≤2.5 µg/L, no. (%)	3 / 11 (27.2%)	36 / 62 (58.0%)	<0.05
Any serum GH ≤1 µg/L, no. (%)	1 / 11 (9%)	29 / 62 (46.7%)	<0.05
Normal serum IGF-1, no. (%)	0	22 / 61 (36.0%)	<0.05
Controlled patients, no. (%)	0	18 / 61 (29.5%)	0.06
Optimally controlled patients, no. (%)	0	19 / 61 (31.1%)	<0.05

Legend: Controlled patients = random serum GH ≤2.5 µg/L and normal IGF-1 for age; optimally controlled patients = any serum GH ≤1 µg/L and normal IGF-1 for age; no.: number; SSA: somatostatin analogs.

Group A

Eleven patients who underwent SSA treatment without previous pituitary surgery had a follow-up of 9.0 ± 4.3 months (range 3–17) and 8 (73%) were on high-dose SSA at the last evaluation. Random GH (median) decreased during SSA from 25.10 µg/L [4.35 – 176] to 12.10 µg/L [0.46–71.1], p=0.09 (Figure 1). IGF-1 (median) decreased from $3.56 \times$ ULN [2.3 – 7.4] to $2.30 \times$ ULN [1.5 – 4.8], p<0.05.

In group A, post-treatment GH levels were independently influenced by post-treatment tumor area (coeff. B=6.6, 95% CI [2.34 – 11.03], p=0.008) and with age at diagnosis (coeff. B=-0.95, 95% CI [-1.82 – -0.09], p=0.03), i.e. younger age and larger tumor area were correlated to higher post-treatment GH levels. Post-treatment IGF-1 levels were independently related to post-treatment tumor area (coeff. B=0.35, 95%CI [0.12 – 0.59], p=0.008)

Group B

Sixty-two patients treated after pituitary surgery were followed for a period of 17.2 ± 10.8 months (3–44), longer than for non-operated patients (p <0.05). The percentage of patients on high-dose SSA at the last evaluation was 60%, similar to that in non-operated patients. Thirty-six patients were assessed on treatment with LAN-SR and 26 patients on treatment with OCT-LAR.

Random GH levels (median) decreased from 6.8 µg/L [1.2–162] to 2.0 µg/L [0.1–64], p <0.01; IGF-1 levels (median) decreased from $2.20 \times$ ULN [0.5–9.4] to $0.49 \times$ ULN [0.4 – 4.1], p<0.01.

In group B, post-treatment GH levels correlated independently only with pre-treatment GH levels, coeff. B=0.21, 95%CI [0.11–0.30], p<0.001. Post-treatment IGF-1 levels correlated with pre-treatment IGF-1 levels (coeff. B=0.28, 95%CI [0.15 – 0.42], p <0.001) and were inversely correlated to age at diagnosis (coeff. B= -0.02, 95% CI [-0.04 – -0.006], p=0.008).

Although pre-SSA treatment random GH levels were not significantly different in operated *versus* non-operated patients, pre-treatment IGF1 levels were higher in the non-operated group (Table 1).

The efficacy of SSA treatment was better in patients who underwent pituitary surgery before SSA treatment, as compared to primary SSA treatment: the operated patients achieved lower GH and IGF-1 levels and there were more patients with 'safe' random GH ≤ 2.5 µg/L, with any serum GH ≤ 1 µg/L, with IGF-1 normalization or optimal disease control (any serum GH ≤ 1 µg/L and normal IGF-1) (Table 2).
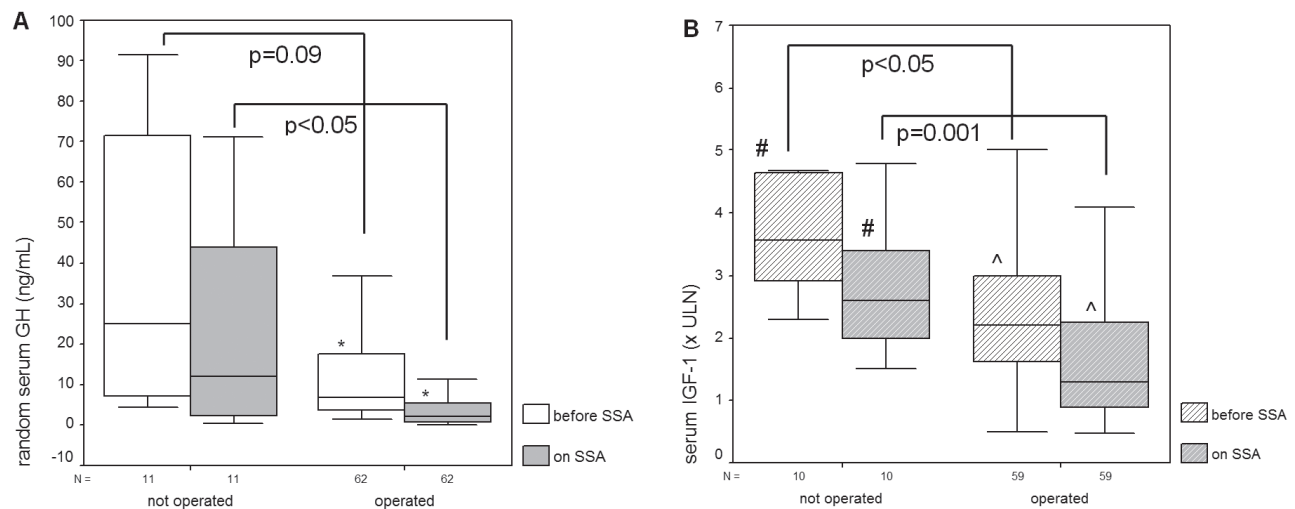

Figure 1. Random serum GH levels (left) and IGF-1 levels (right) before and during treatment with somatostatin analogs (SSA) in patients with acromegaly with or without a previous pituitary surgery. *p<0.01, #p <0.05, ^p <0.001 for levels recorded before SSA versus those during SSA.

Effect of SSA dose increase on GH and IGF-1 secretion

An increase in the SSA dosage was recorded in 43 patients: 8 patients from group A (OCT-LAR 30 mg in all patients) and 35 patients from group B (OCT-LAR 30 mg in 17 patients, LAN-SR 30 mg at 7 days in 14 patients and LAN-SR 30 mg at 10 days in 4 patients). The results are presented in Table 3 and Figure 2.

High-dose SSA induced a significant supplemen-

Table 3. Treatment efficacy of low-dose versus high-dose somatostatin analogs in patients with acromegaly

Parameter	Before SSA *vs* low-dose SSA	p1	Low-dose *vs* high-dose SSA	p2
Random serum GH (µg/L)	7.8 [1.2-176]		4.70 [0.29-98.70]	
Median [range]	3.60 [0.10-98.70]	<0.01	3.35 [0.24-64]	<0.05
	n = 71		n = 43	
Serum IGF-1 × ULN	2.8 ± 1.5		2.3 ± 1.2	
Mean ± SD	1.9 ± 1.2	<0.001	1.9 ± 1.04	<0.05
	n = 65		n = 41	
Random serum GH ≤2.5 µg/L, no./no. evaluable patients (%)	10 / 71 (14.0%)	<0.001	10 / 43 (23.2%)	0.06
	29 / 71 (40.8%)		19 / 43 (44.1%)	
Any serum GH ≤1 µg/L, no./no. evaluable patients (%)	2 / 71 (2.8%)	<0.001	4 / 43 (9.3%)	NS
	25 / 71 (35.2%)		10 / 43 (23.2%)	
Normal serum IGF-1, no./no. evaluable patients (%)	1 / 65 (1.5%)	<0.001	4 / 41 (9.7%)	NS
	18 / 65 (27.6%)		7 / 41 (17.0%)	
Controlled patients, no./no. evaluable patients (%)	0 / 65 (0.0%)	<0.001	0 / 41 (0.0%)	0.059
	12 / 65 (18.4%)		5 / 41 (12.1%)	
Optimally controlled patients, no./no. evaluable patients (%)	0 / 65 (0.0%)	<0.001	0 / 41 (0.0%)	NS
	13 / 65 (20.0%)		4 / 41 (9.7%)	

Controlled patients = random serum GH ≤2.5 µg/L and normal IGF-1 for age; optimally controlled patients = any serum GH ≤1 µg/L and normal IGF-1 for age; p1 = comparison between values before SSA and those after low-dose SSA; p2 = comparison between values on low-dose SSA and those on high-dose SSA; no.: number; SSA: somatostatin analogs.
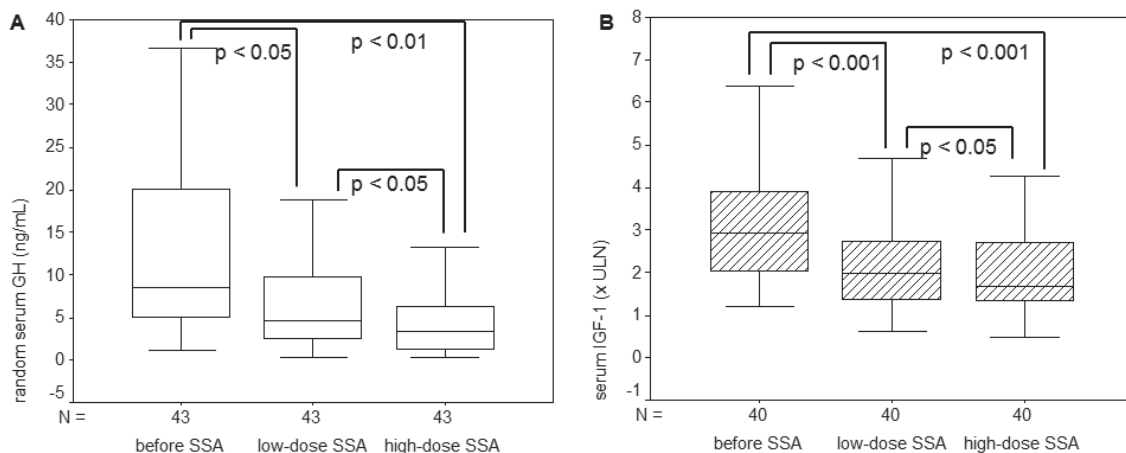

Figure 2. Random serum GH levels (A) and IGF-1 levels (B) before and during treatment with low-dose and high-dose somatostatin analogs (SSA) in patients with acromegaly.

tary decrease of random GH levels and of IGF-1 (xULN), an excess of random GH normalization in 19% of patients, of optimal GH normalization in 14% of patients and of IGF-1 normalization in 9% of patients. High-dose SSA improved the number of controlled patients by 12% (p=0.059) and the number of optimally controlled patients by 9.7%.

In patients evaluated during both low-dose and high-dose SSA (n=43 for GH and 40 for IGF-1), the percentage decrease of random serum GH after high-dose SSA (52 ± 37%) was significantly higher than after low-dose SSA (39 ± 32%, p <0.05), while IGF-1 had a non-significant change (35 ± 26% compared to 31 ± 28%).

High-dose SSA tended to decrease random GH levels (p=0.059) and IGF-1 ($\times$ ULN) (p=0.066) more than low-dose SSA, especially in patients who underwent pituitary surgery (Figure 3), where it also improved the number of controlled patients by 5 (15%) (p=0.053).

Comparison of LAN-SR with OCT-LAR in previously operated patients

An indirect comparison of the two somatostatin analogs in previously operated patients was possible, since 36 patients were evaluated on LAN-SR (36 patients on low dose, 23 patients on high dose) and 26 patients were evaluated on OCT-LAR (24 patients on low dose, 14 on high dose).

The 2 groups did not differ significantly regarding age at diagnosis, tumor characteristics (initial and pretreatment tumor area, invasiveness, % of macroadenomas), pre-treatment random serum GH and IGF-1 levels, although previous radiotherapy was recorded in more patients with LAN-SR (30 patients, 83%) than in those with OCT-LAR (11 patients, 42%), p <0.01.

Treatment efficacy was similar in both groups, i.e. GH levels, IGF-1 levels and the percentage of GH or IGF-1 decrease, whether on low-dose or on high-dose SSA (data not shown).

The frequency of side effects was similar in patients treated with LAN *versus* OCT. The most common complaints, mild in intensity, were: diarrhea in 3 patients (4.1%), constipation in 2 patients (2.7%), floating, abdominal pain in 2 patients (2.7%), nausea in 1 patient (1.3%), and arthralgia in 1 patient (1.7%). Cholelithiasis, including biliary sludge, was detected by ultrasound in 21/73 patients (28%), hyperglycemia in patients without previous diabetes and glucose intolerance was detected in 11 patients (15%), modest hematologic disorders in 13 patients (17.8%), 1 transient eczema in 1 patient (1.7%).

Comparison of LAN-SR with OCT-LAR in the same patient

In 9 patients with previous pituitary surgery one drug was replaced by the other one due to insufficient control of the disease (in all 9) and to a skin
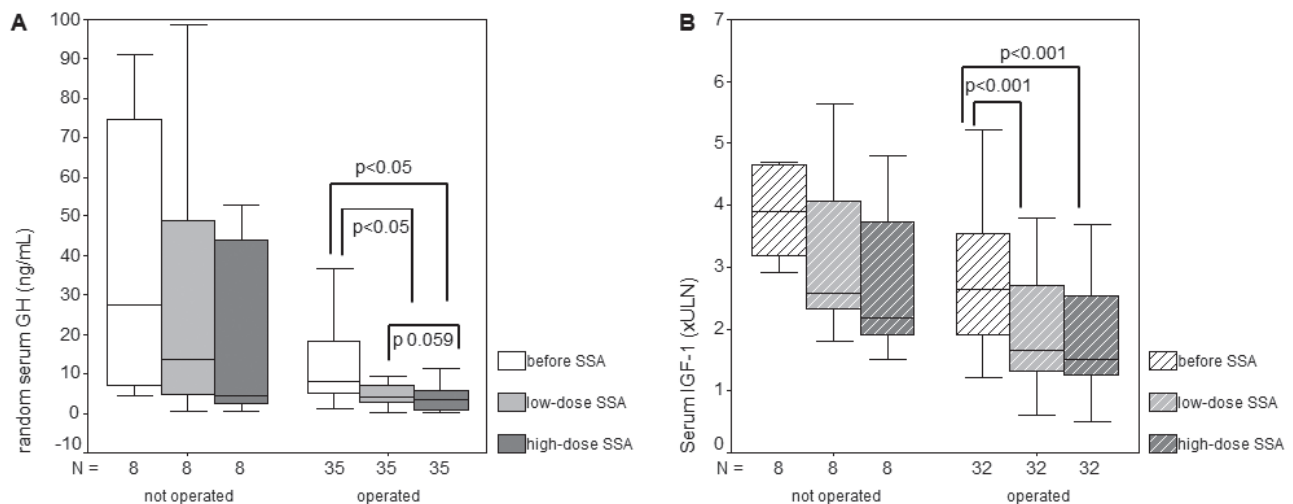

Figure 3. Random serum GH levels (A) and IGF-1 levels (B) before and during treatment with low-dose and high-dose somatostatin analogs (SSA) in patients with acromegaly with or without previous pituitary surgery.

reaction. There were 5 women and 4 men, all with macroadenomas at diagnosis; age at diagnosis was 36 years (22–42 years). We compared similar doses for both drugs, (low doses in 3 patients, high doses in 6 patients) after similar periods of treatment with each drug (3–6 months). All but 1 patient switched from LAN-SR to OCT-LAR. In the patient who switched from OCT to LAN, random GH decreased from 2.59 μg/L after the first drug to 2.1 μg/L on the second drug, while IGF-1 decreased from 3.76 × ULN to 2.4 × ULN.

In 8 patients who switched from LAN to OCT, there was a non-significant reduction of random GH and IGF-1, but GH normalization occurred in 2 more patients (25%) and disease control was attained in 2 patients (25%) (Table 4).

DISCUSSION

SSA efficacy on GH and IGF-1 secretion

Treatment goals in acromegaly include normalization of serum GH and IGF-1 levels, tumor disappearance with normal pituitary function and, finally, improved survival. Surgery is usually the first-line treatment, but frequently adjunctive medical treatment with SSA is used. "Real life" studies with SSA (as our study) reported lower rates of GH and IGF-1 normalization than the controlled ones.[5] In a large UK cohort, 'safe' GH levels actually achieved across all courses of medical therapy were around 75% of cases even in long-term medical treatment courses (>3 years), while GH and IGF-1 both normalized in no more than 55% on SSA.[17] A meta-analysis reviewing more than 600 patients showed GH levels <2.5 μg/L and normal IGF-1 in 57% and 67% of patients, respectively, on Octreotide LAR, and in 48% and 47%, respectively, on Lanreotide depot.[18] In the data from the Belgian Register of Acromegaly,[19] adjunctive medical therapy post-surgery and/or radiotherapy normalized IGF-1 in 53%, GH in 59% and both parameters in 42% of 121 patients. Similarly, in our population of 73 unselected Romanian patients with acromegaly, followed for 16 months, control of GH was attained in 53.4% and normal IGF-1 was recorded in 30.5% of patients. However, according to the latest recommended criteria for disease control, both parameters were normalized only in a quarter of the patients.

The reasons for this apparent "resistance" to SSA could be the lack of compliance of the patient to the therapy, inconsistent monitoring, insufficient dose,

Table 4. Effect of changing LAN-SR with OCT-LAR due to lack of disease control in patients with acromegaly

Patient	Random serum GH (μg/L)					Serum IGF-1 (× ULN)			
	Before SSA 1	On SSA 1	Washout (months)	Before SSA 2	On SSA 2	Before SSA 1	On SSA 1	Before SSA 2	On SSA2
1	146	**24.5**	*3*	146	**18.7**	4	3	4	3.67
2	19.5	**3.6**	*3*	5.9	**1.3**	2	1.1	2.22	0.98
3	5.2	**7.2**	*3*	11.4	**1.2**	3.3	3.18	3.39	1.46
4	3.5	**7.4**	*0*	3.5	**3.3**	2.23	2.07	2.23	1.63
5	6.3	**1.6**	*0*	6.3	**0.5**	1.5	1.5	1.5	0.57
6	7.6	**2.5**	*9*	4.9	**0.77**	1.91	1.87	2.23	1.97
7	160	**36.9**	*8(Re-op)*	70.6	**64**	2.9	2.52	2.93	3.07
8	11.2	**21.13**	*4*	14.6	**21.1**	2.97	2.79	2.8	1.92
Mean ± SD	**44.9±67**	**13.1±13**		33±51	13.8±22	2.6±0.8	2.2±0.7	2.6±0.8	1.9±1
Normal GH ≤2.5 μg/L/Normal IGF-1	-	2		-	4	-	-	-	2
Controlled disease	-	-		-	2				
Optimally controlled	-	-		-	1				

In patient no.7, GH before the first treatment was measured in a different laboratory than the other assessments; the patient was re-operated transphenoidally during the wash-out period (Re-op).

availability of certain therapies (e.g., in Romania the use of SSA as primary therapy is authorized only for large macroadenomas), inter- and intra-variability of common assays for GH and/or IGF-1, tumor phenotype or real drug resistance.[20] The most important factor influencing the treatment outcome is pretreatment GH level, as has been shown in this study and in others.[17]

SSA efficacy in patients treated before or after pituitary surgery

Although some studies reported that preoperative SSA treatment could result in better surgical cure rate in patients with acromegaly, other studies did not support these findings (cited in[19,21]). A recent meta-analysis of 35 studies enrolling 2629 patients showed that surgery was associated with a higher remission rate than primary SSA treatment (67% *vs* 45%; P <0.02), especially in long-term follow-up.[22] SSA pretreatment seems to be beneficial mainly in centers recording a low neurosurgical cure rate.[23]

In our center, patients treated with SSA after pituitary surgery achieved significantly lower GH and IGF-1 levels, while there was a higher percentage of patients with GH ≤2.5 µg/L and with optimal disease control (29%), compared to the primary SSA treatment group, in which none of the patients was optimally controlled. The percentage of patients treated with high-dose SSA was similar between the two groups.

Possible explanations for the better results in operated patients could be a significantly longer duration of SSA treatment (average 17 *vs* 9 months), a smaller tumor mass at treatment initiation (1.2 *vs* 3.8 cm²) or more frequent radiotherapy (in 66% *vs* 9% of patients) in this group. The small number of patients treated pre-operatively[11] is also a limit of this comparison. However, it appears that pituitary surgery and radiotherapy, albeit apparently unsuccessful, may enhance the control achieved on SSA treatment, as has also been suggested by other authors.[17]

Effect of SSA dose increase on GH and IGF1 secretion

Recent guidelines suggest that in patients with inadequate control after 6 months of SSA treatment, dose escalation of SRL therapy should be performed at 3-month intervals based on patient response.[5] There was no increase in the incidence of the adverse events with SSA dose escalation, compared with conventional doses, even on high doses of SSA (e.g., OCT LAR up to 60 mg/28h).[4,15] A 2-year dose-escalation study using Octreotide LAR as first-line therapy in 56 patients with acromegaly demonstrated a clear benefit of dose increase from 20 mg/month to up to 40 mg/month: 86% of patients attained GH levels of <2.5 µg/L, 84% achieved normal IGF-1 levels and 21/32 (65%) of inadequately controlled patients finally achieved remission.[24] Similarly, in our patients high-dose SSA used in 43/73 patients improved the number of controlled patients by 5 (12.1%, p=0.059).

Comparison of LAN-SR with OCT-LAR

In this study we observed that OCT-LAR and LAN-SR are equivalent in reducing GH and IGF-1 levels in operated patients. In 8 patients who switched from LAN-SR to OCT-LAR due to incomplete or lack of disease control, 2 of the patients (25%) attained disease control and 2 additional patients (25%) achieved GH normalization after a similar period of follow-up for both drugs and concordant dose level. However, this was not a controlled or head-to-head study and confounding factors cannot be systematically excluded. Data from switching or crossover studies in the literature show that Octreotide LAR efficacy seems to be generally similar to that of Lanreotide ATG and modestly better than that of Lanreotide SR.[25–27]

CONCLUSION

Our study confirmed that somatostatin analogs are effective in the biochemical control of Romanian patients with acromegaly in about 50% of the cases. The treatment response rate could be improved by escalation of the SSA dose or by debulking surgery. Occasionally, substituting one somatostatin analog to another has shown some benefit.

The authors dedicate this paper to Professor Mihail Coculescu, builder of clinical Neuroendocrinology in Romania, inspiring teacher and mentor, who passed away before this paper was published.

CONFLICT OF INTEREST

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