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Discontinuation of somatostatin analogs while acromegaly is in long-term remission

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Abstract
Purpose We aimed to evaluate the disease activity of medically controlled patients with acromegaly after withdrawal of somatostatin receptor ligands (SRL).
Methods Sixteen patients who were on a stable dose of SRL for more than 2 years and had at least 1 year of remission were included in the study. Five patients were on 10 mg, four were on 20 mg and three were on 30 mg of octreotide; whereas for lanreotide, one was on 60 mg, two were on 90 mg, and one was on 120 mg. All patients had received SRL with 28-day intervals. Basal GH, IGF1, glucose-suppressed GH levels were measured with 3-month intervals for a total of 12 months after withdrawal. Sella MRI evaluation was obtained at 6-month intervals. If the nadir GH level after glucose suppression was >1 ng/ml or IGF1 was above the normal limits during the follow-up period, SRL was restarted.
Results Three months after stopping SRL, 10 (63 %) had biochemical disease recurrence. After 12 months of follow-up, in total 13 (81 %) of the patients recurred. The final basal GH levels before withdrawal, basal GH at month-3, and glucose suppressed GH levels were significantly lower in patients with sustained remission ($p = 0.003$, $p < 0.001$, and $p = 0.001$). Basal GH and glucose suppressed GH levels at month-3 were correlated with the basal GH levels at month-0 ($r = 0.6$, $p = 0.008$ and $r = 0.5$, $p = 0.03$).
Conclusion The final GH levels prior to discontinuation of SRL should be taken into consideration in patients with acromegaly in long-term remission. Moreover, the first visit 3 months after withdrawal is critically important for determining the future status of remission.

Keywords Acromegaly · Medical therapy · Somatostatin analogs · Withdrawal · Discontinuation

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Introduction

Acromegaly is a disorder caused by the excessive secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Although it has an insidious onset with a chronic and debilitating nature, it is amenable to treatment. The goals of treatment in acromegaly include removal or reduction in size of the pituitary adenoma, preservation of pituitary functions, normalization of GH and IGF-1 levels, maintaining clinical stability, improving quality of life and reduction in both comorbidities and mortality [1, 2]. The main treatment for acromegaly is pituitary surgery. However, medical therapy is increasingly being used especially for those with macroadenomas, those who did not have remission postoperatively, those who have contraindications for surgery or are unwilling to have surgery, and in those patients with tumors where surgical cure is not expected [1, 2].

Adjuvant therapy with somatostatin receptor ligands (SRL) is the gold standard medical treatment for acromegaly [1, 2]. They maintain reduction in GH and IGF-1 levels with clinical improvement in 50–60 % and tumor shrinkage in up to 80 % of the patients [3–5]. SRLs have additional beneficial effects on comorbidities, they also decrease disease-related mortality [6, 7]. Gastrointestinal adverse effects with SRLs are common but temporary. Cholelithiasis is frequent with use of SRLs but generally it

does not lead to major problems [8]. However, a life-time of periodic injections and adverse effects may impair the quality of life in patients with acromegaly; therefore, patients may be disturbed by long-term use of medical therapy in order to sustain remission. The duration of SRL therapy and the decision as to when and how to discontinue medical therapy is a matter of controversy.

Herein, we aimed to evaluate disease activity of medically controlled patients with acromegaly after withdrawal of SRL to determine a suitable point for discontinuation of medical therapy.

Patients and methods

We reviewed the clinical charts of 150 patients with acromegaly who were on various but stable doses of SRL with 28-day intervals and were being monitored and treated at the Department of Endocrinology and Metabolism, Cerrahpasa Faculty of Medicine. Inclusion criteria were medical therapy with a stable dose and injection interval of SRL for at least 2 years, no history of radiation, and remission for more than 1 year. Acromegaly was considered to be in remission when the circulating IGF-I level was within the normal age and sex-adjusted ranges and random GH measurements were less than 1 ng/ml [5].

Of the 16 patients (female/male: 9/7) who were eligible for inclusion, 12 were under long-acting octreotide treatment and 4 were under lanreotide treatment. Five patients were on 10 mg, four were on 20 mg and three were on 30 mg of long acting octreotide; whereas for lanreotide, one was on 60 mg, two were on 90 mg and one was 120 mg. Six patients were using cabergoline in addition, which was also discontinued.

All the patients read and signed the informed consent forms before enrolling in the study. The Ethics Committee of Cerrahpasa Faculty of Medicine, Istanbul University, approved the study protocol.

Data obtained from the patients' clinical charts included duration of symptoms; diagnosis of acromegaly; remission and medical therapy, tumor size, GH and IGF-1 levels at first diagnosis of acromegaly and before initiation of SRL; and additional demographic data. We also recorded tumor size and final GH and IGF-1 levels before withdrawal of SRL. In addition, we evaluated basal GH after withdrawal, IGF1, and glucose-suppressed GH levels with 3-month intervals for a total of 12 months. Sella MRI evaluations were planned to be obtained at 6-month intervals. If nadir GH level after glucose suppression was >1 ng/ml or IGF1 was above the normal limits during the follow-up period, SRL was restarted.

GH and IGF-1 levels of all patients before and after withdrawal of SRL were assessed in the same laboratory using the same assays. Procedures for both IGF-1 and GH were based on the use of a one-step chemiluminescence sandwich assay using directly coated magnetic microparticles on a Liaison autoanalyzer (DiaSorin, Saluggia, Italy) and the results were expressed in ng/ml. The detection limit of the GH assay was 0.009 ng/ml and the measuring range was 0–80 ng/ml. The inter- and intra-assay coefficients of variation were 2.5 and 3.9 %, respectively. The detection limit of the IGF-1 assay was <3 ng/ml and the measuring range was 3–1,500 ng/ml. The inter- and intra-assay coefficients of variation were 3.8 and 5.5 %, respectively. The normal ranges for IGF-1: age 16–20, 267.5–470.8 ng/ml; 21–24, 149–332 ng/ml; 25–39, 107.8–246.7 ng/ml; 40–54, 92.7–244.6 ng/ml; >55 year 54–204.4 ng/ml. Age-adjusted IGF1 values were calculated by using age-specific reference ranges for our IGF1 assay (xULN IGF1 = patient's IGF1/age-specific upper limit).

The data was statistically analyzed with the SPSS 17.0 package program. The Chi-square test was used for categorical variables. Sample distribution was evaluated with the Kolmogorov–Smirnov test. Continuous independent variables with normal distribution were compared using the student's T test. Those with non-normal distribution were compared using the Mann–Whitney U test and the results were presented as median and interquartile range (IQR). Wilcoxon test was used to compare two related variables with non-normal distribution. Non-parametric repeated measures were evaluated using the Friedman test. Pearson's correlation coefficient was used for calculation of associations between variables. ROC curve analysis was performed to determine a cut-off level of the latest GH for prediction of recurrence. $p < 0.05$ was considered statistically significant.

Results

The mean age of the 16 patients included in the study was 56 ± 11.5 years. Duration between onset of the symptoms and the diagnosis was 36 (16–48) months, time elapsed since diagnosis of acromegaly was 114 (75–189) months and the duration of remission was 29.5 (16.8–56.3) months. GH and IGF-1 at diagnosis were 7.2 (IQR 3.1–20 ng/ml) and 600 ng/ml (IQR 547-741 ng/ml), respectively, and the largest diameter of adenoma was 15 mm (IQR 14–22 mm).The median xULN IGF-1 at diagnosis was 2.5 (IQR 2.1–2.7).

Of the 16 patients, only 1 had not undergone surgery for the pituitary adenoma. The final median GH and IGF-1 levels prior to initiating SRL were 9.3 (IQR 3.7–18.1 ng/ml) and 600 ng/ml (IQR: 460–756 ng/ml), respectively. The median xULN IGF-1 prior to initiating SRL was 2.4

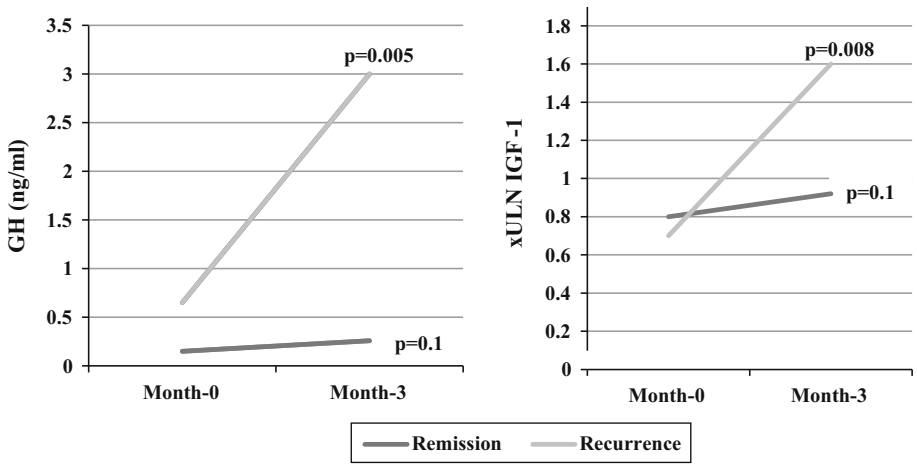

Fig. 1 Change in GH and IGF-1 levels 3 months after withdrawal of SRL

(IQR 1.9–2.9). The SRL median initiation was at 18 months (IQR 1.3–81 months) after the first diagnosis of acromegaly, and total median duration of medical therapy was 95 months (IQR 64.8–135 months) in the entire cohort.

In the entire group, the final median basal GH levels prior to withdrawal of SRL were 0.4 ng/ml (IQR 0.2–0.7 ng/ml), IGF-1 levels were 175.2 ng/ml (IQR 136.9–189.7 ng/ml) and, xULN IGF-1was 0.7 (IQR 0.6–0.9).

Three months after withdrawal, the median GH increased to 1.4 ng/ml (IQR 0.4–3.3 ng/ml) and IGF-1 to 256.1 ng/ml (IQR 186.3–376 ng/ml) (for GH $p < 0.001$ and for IGF-1 $p = 0.001$). xULN IGF-1 increased to 1.1 (0.9–1.8) ($p = 0.001$). Of the 16 patients 10 (63 %) recurred after 3 months of withdrawal ($p < 0.001$).

In patients who recurred, GH levels and xULN IGF-1 after first 3 months of withdrawal (month-3) increased significantly compared with those before withdrawal (month-0) ($p = 0.005$ and $p = 0.008$) (Fig. 1).

When patients with and without sustained remission were compared, the final basal GH levels at month-0, basal GH at month-3 and glucose suppressed GH levels were significantly lower in patients with sustained remission ($p = 0.003$, $p < 0.001$ and $p = 0.001$). Although baseline xULN IGF-1 at month-0 was similar between the groups, xULN IGF-1 at month-3 was lower in cases with sustained remission ($p = 0.6$ and $p = 0.007$, respectively) (Table 1). There was no significant difference between patients with and without sustained remission in other variables and demographic features (Table 1).

Both basal GH and glucose suppressed GH levels at month-3 were positively correlated with the final basal GH levels at month-0 ($r = 0.6$, $p = 0.008$ and $r = 0.5$, $p = 0.03$). Neither basal nor glucose suppressed GH levels after 3 months of withdrawal were correlated with age, duration of symptoms; diagnosis; remission and medication, tumor size, GH and IGF-1 levels at first diagnosis or before initiation of SRL. The IGF-1 levels at month-3 were not associated with the final IGF-1 levels at month-0 or any other characteristics of the patients (data not included).

After 6 months, basal or glucose supressed GH levels and IGF-1 levels did not show a significant change ($p = 0.3$, $p = 0.3$, and $p = 0.7$, respectively). Also the median xULN IGF-1 did not change ($p = 0.8$). Of the six patients who had sustained remission after 3 months, two recurred after a total of 6 months of withdrawal. After 9 months, one patient recurred, whereas three patients had sustained remission. None had recurrent disease activity after 12 months of follow-up (Fig. 2). Comparisons of GH and IGF-1 levels, ACROQOL scores and largest tumor size from the beginning of the 6th month until the end of 12 months are presented in Table 2.

After 3 months of withdrawal, 4 (67 %) of the six patients who were initially on a low dose of SRL (five on 10 mg of octreotide and one on 60 mg of lanreotide) had sustained remission, whereas 2 (20 %) of the ten patients who were on higher doses of SRL sustained their remission ($p = 0.06$). After 12 months of follow up, two patients (40 %) on a low dose of SRL and 1 (33 %) of the patients on higher doses of SRL had sustained remission ($p = 0.2$).

When the entire group was further stratified by dose of SRL, 67 % of the patients who were on 10 mg octreotide or 60 mg lanreotide (low dose) and 33 % of the patients on 20 mg octreotide or 90 mg lanreotide (intermediate dose) had sustained remission after 3 months of withdrawal. None of the patients on 30 mg octreotide or 120 mg lanreotide (high dose) had remission ($p = 0.09$). After 12 months of remission, rates dropped to 40 % in those who were taking a lower dose and 17 % in patients taking the intermediate dose level ($p = 0.3$).

At the end of the 12-month study period, 3 (19 %) of the 16 patients had sustained remission, whereas 13 (81 %)

Table 1 Comparison of the cases with acromegaly with sustained remission and recurrence after 3 months discontinuation of SRL

	Cases with remission (n = 6)	Cases with recurrence (n = 10)	*p*
Gender (F/M)	2/4	7/3	0.2
Age (years)	51.8 ± 11.7	58.5 ± 11.3	0.3
Time/duration (months)[a]			
From onset of symptoms to the diagnosis	24 [7–42]	36 [22–60]	0.3
Since diagnosis	96 [66–168]	132 [81–195]	0.4
From diagnosis until medical therapy	48 [1.8–84]	11 [1–93]	0.7
Medical therapy with SRL	96 [45–126]	95 [74.3–144]	0.8
Remission	33.5 [15.8–51]	25.5 [17.3–61.8]	0.9
Surgery (n, %)	5 (83 %)	10 (100 %)	
Medical treatment with SRL			0.05
Octreotide-LAR			
10 mcg	3 (50 %)	2 (20 %)	
20 mcg	0 (0 %)	4 (40 %)	
30 mcg	0 (0 %)	3 (30 %)	
Lanreotide			
60 mcg	1 (17 %)	0 (0 %)	
90 mcg	2 (33 %)	0 (0 %)	
120 mcg	0 (0 %)	1 (10 %)	
Cabergoline (n, %)	1 (17 %)	5 (50 %)	0.2
Hypopituitarism (under replacement therapy)			
None	5 (83 %)	7 (78 %)	0.4
Thyroid axis	11 (22 %)	0 (0 %)	
Steroid axis	1 (11 %)	1 (17 %)	
Largest tumor diameter (mm)[a]			
At first diagnosis	15.5 [12.8–19]	15 [14–23]	0.8
At initiation of SRL	N/A	N/A	–
At month-0	5 [5–9]	6 [2–7.8]	1
At month-3	N/A	N/A	–
GH levels (ng/ml)[a]			
At first diagnosis	5.7 [2.2–16.8]	8.8 [3.1–30.8]	0.5
At initiation of SRL	4.7 [2.2–16.8]	9.8 [5.6–19.6]	0.4
At month-0	0.2 [0.1–0.2]	0.7 [0.4–0.9]	**0.003****
At month-3	0.3 [0.1–0.6]	3 [1.4–3.8]	**<0.001****
Post–OGTT nadir GH[a] (ng/ml)	0.2 [0.1–0.4]	2.6 [1.3–3.5]	**0.001****
IGF-1 levels (ng/ml)[a]			
At first diagnosis	600 [556–756]	600[520–736]	0.8
xULN:	2.5 [2.1–2.5]	2.5 [2.1–2.9]	1
At initiation of SRL	756 [478–914.5]	560 [450–663.3]	0.3
xULN:	2.5 [1.9–3.4]	2.2 [1.9–2.6]	0.5
At month-0	178.3[156.5–191.9]	143.3 [133.4–193.2]	0.6
xULN:	0.8 [0.7–0.9]	0.7 [0.6–0.9]	0.6
At month-3	187.9 [167.3–241.9]	317.9 [254.3–522.3]	**0.02****
xULN:	0.92 [0.8–0.99]	1.6 [1.1–2.1]	**0.007****

N/A not available, *OGTT* oral glucose tolerance test (75 mg)

Bold values indicate statistically significant

[a] Data was expressed as median and IQR

recurred. Of the 13 patients with recurrence, 10 (77 %) recurred after 3 months, 2 (15 %) after 6 months, 1 (8 %) after 9 months, and none after 12 months of follow up. Moreover, 10 (77 %) of the 13 patients had increased GH and IGF-1 levels, whereas 3 (23 %) only had increased GH levels. None of the patients solely had an increment in IGF-1 levels.

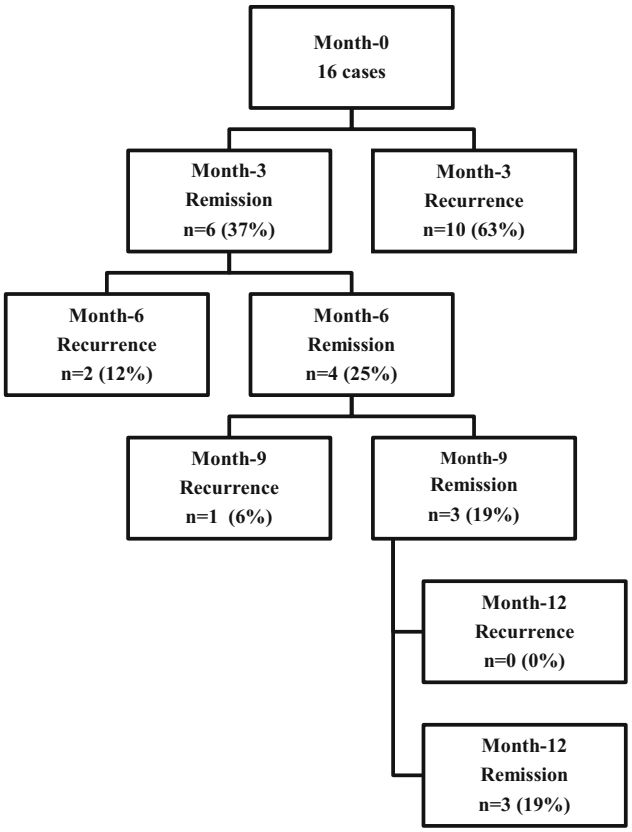

Fig. 2 Number of patients with sustained remission and recurrence with 3 months interval during the study period

Discussion

In the present study, recurrence in biochemical disease activity occurred in 81 % of the patients after withdrawal of somatostatin analogs, and 77 % of the recurrences were seen after the first 3 months. Of the patients with recurrence, 77 % occurred with a concomitant increment in GH and IGF-1 levels, while the other 23 % recurred only with increased GH. The final basal GH prior to withdrawal somatostatin analogs seemed to be predictive of early recurrence.

SRLs, namely long-acting octreotide and lanreotide, are the preferred medical therapy for acromegaly [9–11]. SRLs, acting directly on somatostatin receptors expressed by GH-secreting adenomas, have both antisecretory and antiproliferative effects [12]. The antiproliferative effect is mainly cytostatic, although some apoptotic effect has been shown in certain subtypes [13, 14]. However, for various reasons it is a concern of clinicians whether these antisecretory and antiproliferative effects are permanent after SRLs are withdrawn. First, the indefinite use of SRLs may be disturbing for the patients and a lifetime of periodic injections may impair their quality of life. Second, continuous treatment with injections would cause unnecessary burdens both for patients and healthcare providers if there were ongoing remission after withdrawal of SRLs. Therefore; persistence of remission without medications needs to be assessed, especially in patients whose disease has been well-controlled over a long period. Designation of a certain washout period is an important issue during long-term treatment of acromegaly in order to clarify whether or not the sustained remission is dependent on continuation of SRL treatment. Accordingly, this makes the following a current issue: For how long must therapy with SRLs continue? In which patients can SRLs be withdrawn? When and how can medical therapy be discontinued while preserving remission?

In the current study, the majority of patients who achieved remission during long-term treatment with SRLs recurred after withdrawal. The 12-month follow-up period showed that 81 % of the patients recurred. This rate was in concordance with the results of previous studies, which also included data on long-term follow-up after withdrawal of SRLs [3, 15–17]. In the current study, the criteria for the selection of patients and for remission were more strict. Previous studies evaluated remission possibility based on injection intervals of SRLs, and showed that longer injection-intervals were associated with sustained remission [15, 17]. However, we only included the patients who had injections with 28-day intervals, without previously prolonged injection intervals. Patients with previous radiotherapy or radiosurgery were excluded in order to be able to define the impact of postoperative adjuvant treatment with SRLs alone. Moreover, unlike previous studies, GH

Table 2 GH, IGF-I,ACROQOL scores and size of residual adenoma from month-6 through month-12

	Month- 6	Month- 9	Month-12	*p*
GH (ng/ml)	0.5 [0.2–1.6]	0.3 [0.1–1.4]	0.2 [0.1–0.3]	0.9
IGF-I (ng/ml)	203.5 [138.2–266]	198.3 [176.3–322.6]	209 [157–235]	0.9
xULN IGF-1	0.8 [0.7–1.1]	0.9 [0.8–1.3]	0.9 [0.6–0.9]	0.7
ACROQOL	91 [67–95]	77 [66.3–92.3]	93 [59–96]	0.6
Largest tumor diameter (mm)	5.9 [5.7–6]	–	5 [5–5]	–

The results are presented as median and interquartile range (IQR)

* *p* values represent comparison of variables from month-0 through month-12 (compared by Friedman Test)

levels below 1 ng/ml were accepted as a remission criterion instead of 2.5 ng/ml, and only levels of IGF-1 within normal limits of age and sex were considered to show remission [5].

In the current study, although the patients were on variable doses of SRL, the injection intervals were stable. The analysis of patients with sustained remission after 3 months showed those on lower doses of SRL tended to have a higher rate of early remission after withdrawal compared with those on higher doses of SRL. This confirms recent findings in the field of acromegaly treatment with SRLs [15, 17].

After 12 months of follow up, there was no difference in remission rates when the patients were stratified by dose of SRL. Accordingly, although the dose of SRL, independent of the interval, may predict early sustained remission, this may not be the case for long-term withdrawal of SRLs. It is also noteworthy that four patients were on a high dose of SRL and none of these patients sustained their remission for more than 3 months. This finding was in line with previous studies that reported low-dose SRL was a predictive factor for remission after SRL withdrawal. However, none of the earlier studies attempted to withdraw high-dose SRLs, the previous findings were based on withdrawal of lower doses [15–17].

A significant proportion of recurrence occured after the first 3 months of withdrawal. Previous studies with follow up of 12 months or less have shown early recurrence after withdrawal of SRL [3, 15, 17–19]. Likewise, in the curent study, disease recurred after 3 months in 68 % of the patients. Moreover, 77 % of the recurrences occured during the first 3 months and the recurrence rate dropped significantly in the subsequent months.

Interestingly, 77 % of the recurrences occured with an increment of GH and IGF-1, and the remaining 23 % only had increased GH. None of the patients recurred due to increased IGF-1 alone. In all patients, recurrence was due to a loss of biochemical control, none had clinical detorioration or tumor regrowth. Recurrence was also reported to be due to concurrent increased GH and IGF-1 levels in the majority of the previous SRL withdrawal studies [3, 18, 19]. It is difficult to explain why IGF-1 levels were normal despite increased GH levels in those with GH and IGF-1 discrepancy. However, the explanation of such discrepancies was not an endpoint in the study design, more data is necessary in order to explain the discordant GH and IGF-1 levels in this subgroup of patients.

GH levels prior to withdrawal and at month-3, and glucose suppressed GH levels at month-3 were significantly higher in patients with recurrence compared with those in patients with sustained remission. Although IGF-1 levels after withdrawal were higher in cases with recurrence, IGF-1 levels prior to withdrawals were not different between patients with sustained remission and recurrence. Moreover, all patients whose basal GH levels were higher prior to withdrawal led to both higher basal and postglucose suppressed nadir GH levels after 3 months of withdrawal. When these findings are taken into consideration, together with the fact that a considerable proportion of patients recurred based on the GH criterion alone, higher levels of GH were thought to be a determinant of future recurrence. In contrast to the previous studies, which suggested that IGF-1 was a more important determinant for remission and/or recurrence, IGF-1 levels did not predict recurrence as much as GH in the current study [3, 15, 17, 19].

In conclusion, in certain patients with long-term remission of acromegaly it is feasible to discontinue medical therapy with somatostatin analogs. The first visit 3 months after withdrawal is critically important to determine the future status of remission. Moreover, current GH levels may predict successful control of biochemical diasease activity after withdrawal of somatostatin analogs in patients with well-controlled acromegaly. Therefore, the most recent GH levels should be taken into consideration prior to discontinuation of somatostatin analogs in patients with acromegaly who are in long-term remission.

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Conflict 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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