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Predictive Factors of Somatostatin Receptor Ligand Response in Acromegaly—A Prospective Study

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Abstract

Context: Somatostatin receptor ligands (SRLs) are the cornerstone medical treatments for acromegaly; however, many patients remain unresponsive to SRLs. Well-established predictive markers of response are needed.

Objective: We aimed to explore the relationship between responsiveness to SRLs relative to somatostatin (SST)2A and 5 receptor expression, adenoma granularity, and T2-weighted magnetic resonance imaging (MRI) signal intensity (T2WSI).

Methods: We conducted a multicentric, prospective, observational cohort study, in France. Forty-nine naïve patients (ie, patients without preoperative SRL treatment) with active acromegaly following surgery were treated with octreotide (group 1; n=47), or pasireotide if uncontrolled under first-generation SRLs (group 2; n=9). Data were collected at baseline and months 3 and 6. Biochemical measurements, immunohistochemistry studies, and MRI readings were centralized.

Results: In group 1, IGF-I decrease from baseline to month 6 positively correlated with SST2A immunoreactive score (IRS), $P=0.01$. Densely granulated/intermediate adenomas had a greater IGF-I and GH decrease under octreotide compared with sparsely granulated adenomas ($P=0.02$ and $P=0.006$, respectively), and expressed greater levels of SST2A ($P<0.001$), coupled with lower levels of SST5 ($P=0.004$). T2WSI changed between preoperative MRI and month 6 MRI in one-half of the patients. Finally, SST5 IRS was higher in preoperative hyperintense compared with preoperative hypointense adenomas ($P=0.04$), and most sparsely granulated and most hyperintense adenomas expressed high SST5 levels.

Conclusion: We prospectively confirm that SST2A and adenoma granularity are good predictors of response to octreotide. We propose the IRS for scoring system harmonization. MRI sequences must be optimized to be able to use the T2WSI as a predictor of treatment response.

Key Words: acromegaly, octreotide, somatostatin receptor, growth hormone (GH), insulin growth factor-I (IGF-I)

Abbreviations: IHC, immunohistochemistry; IRS, immunoreactive score; LAR, long-acting release; M, month; MRI, magnetic resonance imaging; SRL, somatostatin receptor ligand; SST, somatostatin; T2WSI, T2-weighted magnetic resonance imaging signal intensity.

Acromegaly is a chronic disease resulting from GH hypersecretion and subsequent excessive production of IGF-I (1); a GH-secreting adenoma contributes to >95% of cases (1, 2). In the absence of biochemical control, prolonged GH and

IGF-I excess in adults leads to numerous systemic complications, increased mortality, and decreased quality of life (3).

Surgical resection is the recommended first-line treatment, where possible (4); surgical cure is achieved in less than two-

thirds of patients (5, 6). In case of persistent disease following surgery, the recommended first-line medical therapy consists of first-generation long-acting release (LAR) somatostatin receptor ligands (SRLs) (ie, octreotide or lanreotide) (4). These molecules target preferentially somatostatin (SST) receptor subtype 2 (7, 8) and allow normalization of GH and IGF-I in approximately 45% of cases (9). Second-line medical therapies include pasireotide, a second-generation SRL that targets SST1, SST2, SST3, and especially the SST5 receptor (8, 10). Pasireotide LAR was more effective than octreotide LAR in achieving biochemical control in patients with medically naïve acromegaly (11) and led to normalization of GH and IGF-I in 20% of patients who were inadequately controlled using first-generation SRLs (12). Impaired glucose metabolism was also more frequent with pasireotide LAR (11, 12).

Among the factors to consider when choosing a medical treatment, the 2018 expert consensus included predictive factors of treatment response, notably adenoma granularity and T2-weighted magnetic resonance imaging (MRI) signal intensity (T2WSI) (4); both densely granulated adenomas (4, 13–15) and hypointense adenomas (4, 16–18) were shown to exhibit a greater response to first-generation SRLs. However, evidence regarding the predictive role of SST2A and SST5 receptor expression via immunohistochemistry (IHC) was considered of very low quality, lacking scoring harmonization and prospective validation (4). Indeed, although SST2A receptor expression was consistently found to positively correlate or to be associated with the biochemical response to first-generation SRLs (14, 19–25), the studies analyzing the predictive role of SST2A and SST5 receptor expression are all retrospective, reported differently the level of expression of SST receptors, and some included patients who received preoperative SRL treatment, which might modify SST2A receptor expression (19, 20, 26). Studies assessing the biochemical response to pasireotide relative to SST2A and SST5 receptor expression are scarce and yielded contradictory results (24, 27).

Here, we aimed to prospectively assess the relationship between response to first- and second-generation SRLs and SST2A and SST5 receptor expression, adenoma granularity, and T2WSI, in exclusively naïve patients (ie, patients without preoperative SRL treatment). Furthermore, we explored the relationship between SST receptor expression and adenoma granularity, SST receptor expression and T2WSI, and between adenoma granularity and T2WSI.

Methods

Patients and Study Design

This is a longitudinal, observational, prospective cohort study conducted from 2017 to 2020 in 14 clinical centers in France. The study included adult acromegaly patients who were inadequately controlled by surgery and who were to be initiated on either octreotide LAR or pasireotide LAR for the first time. The patients were treated according to each center's protocol.

Group 1 included patients who were to receive octreotide LAR IM (starting dose, 10–30 mg/28 days). Group 2 included patients who were unresponsive to a first-generation SRL administered for at least 3 months but not more than 12 months and were to receive pasireotide LAR IM (starting dose 40 mg/28 days). Group 1 was allowed to join group 2 in case octreotide LAR was switched to pasireotide LAR before the end of the inclusion date in group 2 (in this case, these patients

were first analyzed as being part of group 1, and then of group 2). The study required an assessment at baseline (M0), month 3 (M3), and 6 (M6). The study accepted an offset of the visit dates by at most 1 month.

The study was performed in line with the principles of the Declaration of Helsinki and its later amendments, it was approved by the bioethics committee “Comité de protection des personnes Sud-Méditerranée II” (no. 2017-A00938-45), and registered with “Commission nationale de l'informatique et des libertés” no. 2002304. Informed consent was obtained from all patients before enrollment.

Biochemical Assessment

Laboratory parameters (GH, IGF-I) were measured centrally at M0, M3 and M6, using Immulite Siemens Healthcare Diagnostics Products (Llanberis, UK) chemiluminescent immuno-metric assays (Siemens catalog #L2KGF2, RRID:AB_2756880 for IGF-I, and Siemens catalog #L2KGRH2, RRID:AB_2811291 for GH). Note that “RRID:AB_2756880” is hyperlinked to https://scicrunch.org/resolver/AB_2756880 and “RRID:AB_2811291” is hyperlinked to https://scicrunch.org/resolver/AB_2811291. For GH, the intra- and interassays coefficients of variation were respectively 3.5% and 6.5% for 2.6 ng/mL, and 2.9% and 4.2% for 7.5 ng/mL, expressed relative to World Health Organization Second International Standard 98/574. For IGF-I, the intra- and interassays coefficients of variation were respectively 6.3% and 7.6% for 56 ng/mL, and 3.1% and 3.9% for 200 ng/mL, expressed relative to World Health Organization First International Standard 02/2547. The detection limits were 0.01 ng/mL for GH and 3 ng/mL for IGF-I. Normal levels of IGF-I were sex- and age-adjusted (28).

Results are presented as percent reduction of GH and IGF-I between M0 and M6. M6 GH measurements were replaced with M3 GH measurements if the treatment was stopped before M6. Acromegaly control was defined as both normalized IGF-I and random GH < 1 µg/L; partial response was defined as a > 20% decrease in IGF-I, and resistance was defined as a ≤20% decrease in IGF-I.

Magnetic Resonance Imaging

Invasion of the adenoma into the cavernous sinus (revised Knosp classification (29)), T2WSI, and change in signal from the preoperative MRI to M6 were evaluated centrally, in a blinded manner, by 2 pituitary imaging experts. T2WSI was evaluated qualitatively as described by Potorac et al (30), and classified as hypointense, isointense, hyperintense, and heterogeneous/not interpretable (Fig. 1). In case of discordance between the 2 experts, the evaluation was jointly repeated to reach consensus.

Histopathology and Immunohistochemistry

Automated IHC staining to determine SST2A and SST5 receptor expression, and adenoma granularity, was performed centrally by a single pathologist (at once for all patients), and subsequently assessed centrally by 2 expert assessors. In case of discordance between the 2 experts, the staining was jointly reviewed to reach consensus. Antibodies used for IHC were as follows: SST2A (1:4000, rabbit monoclonal, clone UMB-1, Abcam, Cambridge, UK, Abcam catalog #ab134152, RRID:AB_2737601), SST5 (1:500, rabbit monoclonal, clone UMB-4, Abcam, Cambridge, UK, Abcam catalog #ab109495, RRID:AB_10859946), and

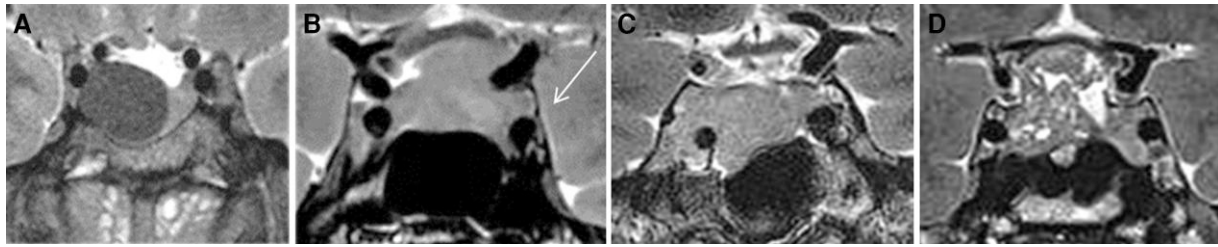


Figure 1. (A) Hypointense, (B) isointense, (C) hyperintense, and (D) heterogeneous T2-weighted MRI signal intensity. The white arrow indicates the cortex of the temporal lobe (B).

cytokeratin 18 (1:50, mouse monoclonal, clone DC10, Dako, Glostrup, Denmark, Agilent catalog #M7010, RRID: AB_2133299). Note that “RRID:AB_2737601” is hyperlinked to https://scicrunch.org/resolver/AB_2737601, “RRID:AB_10859946” is hyperlinked to https://scicrunch.org/resolver/AB_10859946, and “RRID:AB_2133299” is hyperlinked to https://scicrunch.org/resolver/AB_2133299. The IHC protocol was the same as previously published (31).

SST2A and SST5 receptor expression was assessed using the immunoreactive score (IRS), as previously published (31, 32). Briefly, the IRS (0-12) is the product between the percentage of stained cells (0-4: 0=0% stained cells, 1 ≤ 10%, 2 = 10%-50%, 3 = 51%-80%, 4 ≥ 80%) and the staining intensity (0-3: 0 = absent, 1 = weak, 2 = moderate, 3 = strong). According to cytokeratin 18 IHC distribution pattern, adenomas were categorized into densely granulated (perinuclear pattern), intermediate (transitional pattern), and sparsely granulated adenomas (dot-pattern, fibrous body) (33). The first 2 categories were merged into 1 category for analysis, as previously done in the literature (14, 15).

Statistical Analysis

All analyses related to treatment response were conducted separately in groups 1 and 2, whereas analyses looking at baseline characteristics were performed on all unique patients for which adenoma tissue was exploitable. Spearman correlation, Mann-Whitney, Kruskal-Wallis, exact Fisher test, and receiver operator characteristic curve analysis, were applied, as appropriate. The significance level was set at 5% for all tests. Statistical analysis and graphs were made using SAS v9.4 software.

Results

Patients and Tumors Characteristics

A total of 49 patients were recruited: group 1 included 47 patients and group 2 included 9 patients (Fig. 2), 7 of which switched from group 1. Adenoma tissue was not exploitable in 9 patients. The final study cohort consisted of 39 patients (group 1) and 8 patients (group 2); there was a total of 41 unique patients for which adenoma tissue was exploitable. One patient from group 1 did not finish the study because of adverse events, and 2 patients (1 from each group) did not finish the study because of insufficient efficacy of the treatment (Fig. 2). Table 1 provides details of the patients and tumors characteristics per group.

Treatment Efficacy

Twelve patients (30.8%) had a dose change in group 1: 11 because of insufficient control (all 11 of these cases received an

initial dose of 20 mg/28 days and were switched to 30 mg/28 days after 2 injections in 1 case, after 3 injections in 2 cases, after 4 injections in 7 cases, and after 5 injections in 1 case, respectively), and 1 because of an adverse event (this patient received an initial dose of 20 mg/28 days and was switched to 10 mg/28 days after 4 injections). Two patients (25%) had a dose change in group 2 because of insufficient control: both patients received an initial dose of 40 mg/28 days and were switched to 60 mg/28 days after 4 injections. The maximum dose was 30 mg in group 1 and 60 mg in group 2. The median final dose was 30 mg/days in group 1 (73% of patients had a final dose of 30 mg/28 days in group 1) and 40 mg/28 days in group 2 (71.4% of patients had a final dose of 40 mg/28 days in group 2).

At M6, no patient achieved biochemical control. In group 1, partial response was observed in 10/35 (28.6%) patients, and resistance was observed in 25/35 (71.4%) patients. In group 2, 3/6 (50%) patients had a partial response, and 3/6 (50%) patients were resistant.

The median percent reduction of IGF-I from M0 to M6 was 19.7% (range, -107.6 to 66.8) in group 1 and 32.7% (range, 2.5-65.7) in group 2, whereas the median percent reduction of GH from M0 to M6 was 52.9% (range, -1154.5 to 93.2) in group 1 and 67.5% (range, 33.6-83.3) in group 2. Given that group 2 was formed by only 6 patients at M6, we will only report the analyses exploring the relationships between response and potential predictive factors of response for this group in Table 2.

Octreotide Efficacy Relative to SST2A and SST5 Receptor Expression

In group 1, there was a positive, moderate correlation between SST2A IRS and the percent reduction of IGF-I from M0 to M6 (Fig. 3A). No statistically significant correlation between SST2A IRS and the percent reduction of GH from M0 to M6 was found ($\rho = 0.25$, $P = 0.12$). Moreover, SST5 IRS did not correlate with the percent reduction of IGF-I from M0 to M6 (Fig. 3B), or with that of GH ($\rho = -0.16$, $P = 0.34$). Similar to the SST2A IRS analyses, there was also a positive, moderate correlation between SST2A IRS/SST5 IRS ratio and the percent reduction of IGF-I from M0 to M6 (Fig. 3C); no statistically significant correlation between SST2A IRS/SST5 IRS ratio and the percent reduction of GH from M0 to M6 was found ($\rho = 0.32$, $P = 0.06$).

Interestingly, when analyzing together all 41 unique patients, no correlation was found between SST2A IRS and SST5 IRS ($\rho = 0.03$, $P = 0.84$).

Regarding the best SST2A IRS cutoff discriminating between resistant and partial responders to octreotide LAR, in our cohort, the receiver operator characteristic curve analysis

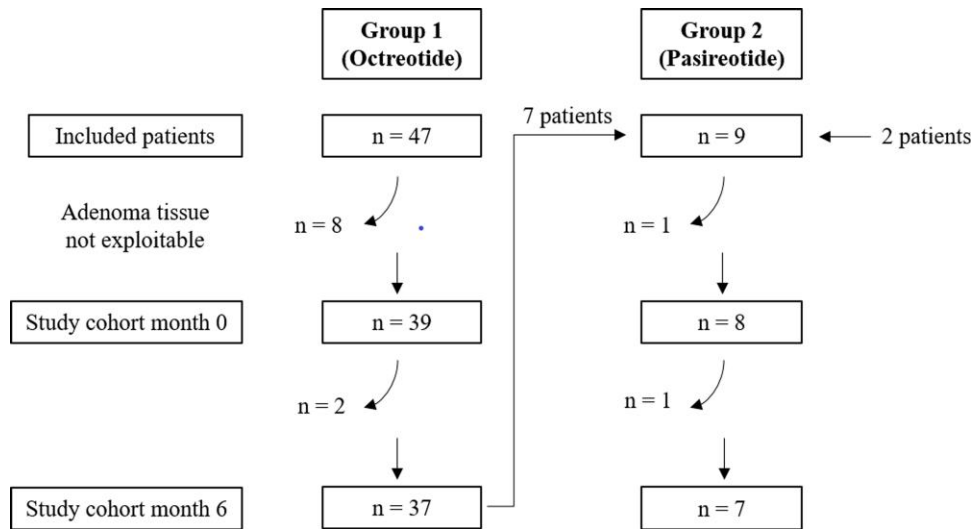


Figure 2. Patient flow in the study.

identified a SST2A IRS ≥ 7 to be the best predictor of response, with 81.25% sensitivity, 58.82% specificity, a positive predictive value of 65%, a negative predictive value of 76.92%, and an accuracy of 69.69% (Fig. 3D).

Octreotide Efficacy Relative to Adenoma Granularity

The densely granulated/intermediate group had a higher percent reduction from M0 to M6 of both IGF-I and GH, compared with the sparsely granulated group, with a median percent reduction of IGF-I of 44.8 vs 14.5, $P = 0.02$, and a median percent reduction of GH of 69 vs 5.9, $P = 0.006$ (Fig. 4).

Interestingly, when analyzing together all 41 unique patients, the densely granulated/intermediate group had higher SST2A IRS, higher SST2A IRS/SST5 IRS ratio, and lower SST5 IRS than the sparsely granulated group, $P < 0.001$, $P < 0.0001$, and $P = 0.004$, respectively (Figs. 5 and 6). Moreover, 76% of sparsely granulated adenomas expressed high levels of SST5 (ie, IRS ≥ 9).

Octreotide Efficacy Relative to T2-weighted MRI Signal Intensity

Neither the percent reduction of IGF-I from M0 to M6, nor that of GH, were statistically different between hypointense (median = 16.4; range, -9.1 to 66.8, $n = 10$ and median = 57.3; range, -51.5 to 93.2, $n = 11$), isointense (median = 26.4; range, -107.6 to 65.4, $n = 6$ and median = 35.8; range, -239.4 to 77.5, $n = 6$), and hyperintense adenomas (median = 40.5; range, 1.3-61.9, $n = 5$ and median = 13.7; range, -43.7 to 91.7, $n = 6$), $P = 0.93$ and $P = 0.82$, respectively.

From interpretable MRI scans, T2WSI changed between the preoperative MRI and the M6-MRI for 6 of 13 (46.1%) patients. This change was either from isointense to hyperintense (3 cases) or to hypointense (1 case), or from hyperintense to isointense (1 case), or from hypointense to hyperintense (1 case).

When analyzing all unique patients together, SST5 IRS was statistically different between hyperintense, isointense, and hypointense adenomas, $P = 0.01$, as evaluated on the preoperative MRIs, with significantly higher SST5 IRS in hyperintense than in hypointense adenomas, $P = 0.04$ (Fig. 7A).

Moreover, 75% of hyperintense adenomas expressed high levels of SST5 (ie, IRS = 12). Neither SST2A IRS nor SST2A IRS/SST5 IRS ratio was statistically different between hypointense, isointense, and hyperintense adenomas (Fig. 7B and C). The granulation pattern was not statistically different between the hypointense, isointense, and hyperintense adenomas, either ($P = 0.15$); however, hypointense adenomas tended to be associated with a densely granulated/intermediate pattern with an odds ratio of 3:1 (Table 3).

Discussion

Here, we conducted the first prospective, longitudinal study to evaluate first- and second-generation SRLs efficacy relative to SST2A and SST5 receptor expression, adenoma granularity, and T2WSI. The strength and originality of our study lies in its prospective, longitudinal design, allowing a detailed description of the enrolled patients, whereas its observational design reflects more closely real life. Furthermore, the exclusive inclusion of treatment-naïve patients averted potential modification of SST receptor expression and of T2WSI by the administration of preoperative SRLs. In addition, centralized biochemical measurements, IHC, and MRI readings add further validity to the outcomes.

SST2A and SST5 receptors are the most frequently expressed SST receptor subtypes in GH-secreting adenomas (34, 35), but the level of expression varies from 1 individual to another (34). Several retrospective studies, mainly conducted with first-generation SRLs, have sought to assess the relationship between the level of expression of SST2A and SST5 receptors and the biochemical response. The studies repeatedly showed that biochemical response to first-generation SRLs positively correlated or was associated with SST2A receptor expression, regardless of the way the level of receptor expression was reported or of the definition used for biochemical response (14, 19–25, 36–38). However, no statistically significant associations or correlations between SST5 receptor expression and the response to first-generation SRLs were found (19, 20, 24, 38). The results regarding the biochemical response to pasireotide LAR are conflicting, with 1 study showing that the response to pasireotide LAR in patients

Table 1. Patient and tumor characteristics

	Group 1 (n = 39)	Group 2 (n = 8)
Sex		
Male (n, %)	24 (61.5%)	7 (87.5%)
Female (n, %)	15 (38.5%)	1 (12.5%)
Age (median with range)	44.5 (21.7-77.1)	38.9 (29.0-46.0)
Type 2 diabetes (n, %)	7 (17.9%)	1 (12.5%)
Months since acromegaly diagnosis (median with range)	6.8 (1.6-128.8)	12.8 (4.5-17.8)
Months since adenoma was surgically removed (median with range)	4.2 (1.3-49.4)	9.8 (3.5-13.4)
Tumor invasion into the cavernous sinus (preoperative MRI)		
Yes (n, %)	12 (30.7%)	3 (37.5%)
No (n, %)	18 (46.2%)	4 (50.1%)
NA (n, %)	9 (23.1%)	1 (12.5%)
T2-weighted MRI signal intensity (preoperative MRI)		
Hypointense (n, %)	11 (28.2%)	3 (37.5%)
Isointense (n, %)	8 (20.5%)	0 (0%)
Hyperintense (n, %)	8 (20.5%)	2 (25%)
Heterogeneous/noninterpretable (n, %)	3 (7.7%)	2 (25%)
NA (n, %)	9 (23.1%)	1 (12.5%)
GH ($\mu\text{g/L}$) at M0 (median with range)	2.9 (0.3-18.8)	3.0 (0.6-44.3)
IGF-I (ng/mL) at M0 (median with range)	420.0 (123-802)	388.0 (274-592)
SST2A receptor IRS (median with range)	9 (0-12)	5 (4-12)
SST5 receptor IRS (median with range)	6 (1-12)	12 (3-12)
Adenoma granularity		
Densely granulated + intermediate (n, %)	16 + 8 (61.5%)	3 + 0 (37.5%)
Sparsely granulated (n, %)	15 (38.5%)	5 (62.5%)
Starting dose		
10 mg/28 d (n, %)	1 (2.6%)	0 (0%)
20 mg/28 d (n, %)	21 (53.8%)	0 (0%)
30 mg/28 d (n, %)	17 (43.6%)	0 (0%)
40 mg/28 d (n, %)	0 (0%)	8 (100%)

Abbreviations: IRS, immunoreactive score; MRI, magnetic resonance imaging; M0, month 0; NA, not available; SST, somatostatin.

resistant to first-generation SRLs was positively associated with SST5 receptor expression, but not significantly associated with SST2A receptor expression (24), whereas another study has reported a positive correlation with SST2A receptor expression in patients partially responsive to first-generation SRLs, but not with SST5 receptor expression (27). However, the sample sizes of both studies were limited (ie, 14 (27) and 11 patients (24)).

Regarding SST2A receptor expression in our study, we observed a positive, moderate correlation between SST2A IRS and the percent decrease of IGF-I in group 1. The correlation

with the percent decrease of GH was not statistically significant. Consistently with the literature and expected given the low affinity of octreotide for SST5, we did not find any correlations between SST5 receptor expression and the percent decrease of IGF-I, or of GH. Moreover, the SST2A IRS/SST5 IRS ratio, similar to SST2A IRS, positively and moderately correlated with the percent decrease of IGF-I in group 1, reinforcing a role for SST2A and the absence of a role for SST5. Our prospective study confirms, therefore, that SST2A receptor expression is a good predictor of biochemical response to first-generation SRLs, whereas SST5 receptor expression is not. It appears reasonable that future consensus/guidelines include SST2 as an established predictive factor of response to octreotide. However, to introduce it in the clinical practice, harmonization of SST expression grading will be needed. So far, the IRS was used in 3 other studies analyzing the relationship between SST2 receptor expression and response to octreotide (20, 21, 38), in addition to ours (all the other scoring systems were used even less frequently (14, 19, 22–25, 37)). Given that the IRS is fairly simple to use and also used in several pituitary adenoma subtypes (31, 39), we propose keeping IRS as the preferred SST scoring system for acromegaly.

Regarding the best SST2A IRS cutoff, in our cohort, an SST2A IRS ≥ 7 best discriminated between resistant and partial responders to octreotide LAR. However, this cutoff should be cautiously interpreted given that we did not see any complete response in our cohort and that we defined a partial response as a $\leq 20\%$ decrease in IGF-I. Indeed, that we did not see any complete response (and that, generally speaking, the response to octreotide was lesser than expected) is a limitation of our study and might be explained by the fact that both the starting dose and the uptitration were performed according to each center's protocol, coupled with a relatively short duration of the study (6 months). Therefore, the final dose might have been insufficient in some patients and/or the duration of treatment on the optimal dose too short.

Regarding adenoma granularity, based on IHC, GH-secreting adenomas can be classified as densely granulated, sparsely granulated, or intermediate (33). The intermediate group is generally considered to behave similarly to the densely granulated one (14, 15, 33); therefore, studies usually considered these 2 subtypes together (14, 15). Densely granulated/intermediate adenomas were shown to be more responsive to first-generation SRLs compared with sparsely granulated adenomas, and in addition, to express the SST2A receptor more frequently and to a greater extent (13–15, 40). Indeed, the better responsiveness of densely granulated adenomas might be due in part to this higher expression of SST2A receptor (14, 15). Regarding the expression of SST5 receptor relative to the granulation pattern, the literature is contradictory, with certain authors demonstrating a similar expression of SST5 between densely granulated and sparsely granulated adenomas (34), whereas others demonstrating SST5 to be expressed only in sparsely granulated adenomas, but not in densely granulated adenomas (41).

In our cohort, densely granulated/intermediate adenomas were also more responsive to octreotide than sparsely granulated adenomas and expressed higher levels of SST2A; moreover, densely granulated/intermediate adenomas also had higher SST2A IRS/SST5 IRS ratio and

Table 2. Response to pasireotide LAR relative to SST expression, adenoma granularity, and T2WSI

Correlation analysis (SST expression)		rho (n = 6)	P value
% reduction of IGF-I from M0 to M6 vs SST2A IRS		0.46	0.33
% reduction of IGF-I from M0 to M6 vs SST5 IRS		-0.36	0.46
% reduction of IGF-I from M0 to M6 vs SST2A IRS/SST5 IRS ratio		0.42	0.38
% reduction of GH from M0 to M6 vs SST2A IRS		-0.06	0.90
% reduction of GH from M0 to M6 vs SST5 IRS		-0.24	0.62
% reduction of GH from M0 to M6 vs SST2A IRS/SST5 IRS ratio		0	1
Association analysis (adenoma granulation pattern)		DG/I (n = 2)	SG (n = 4)
% reduction of IGF-I from M0 to M6 (median with range)		56.8 (47.9-65.7)	16.9 (2.5-50.4)
% reduction of GH from M0 to M6 (median with range)		77.1 (74.1-80.1)	54.5 (33.6-83.3)
Association analysis (T2WSI—preoperative MRI)		Hypointense (n = 3)	Hyperintense (n = 1)
% reduction of IGF-I from M0 to M6 (median with range)		47.9 (2.5-50.4)	17.6
% reduction of GH from M0 to M6 (median with range)		74.1 (41.5-83.3)	33.6

Abbreviations: DG/I, densely granulated/intermediate; IRS, immunoreactive score; LAR, long-acting release; M, month; SG, sparsely granulated; SST, somatostatin receptor; T2WSI, T2-weighted magnetic resonance imaging signal intensity.

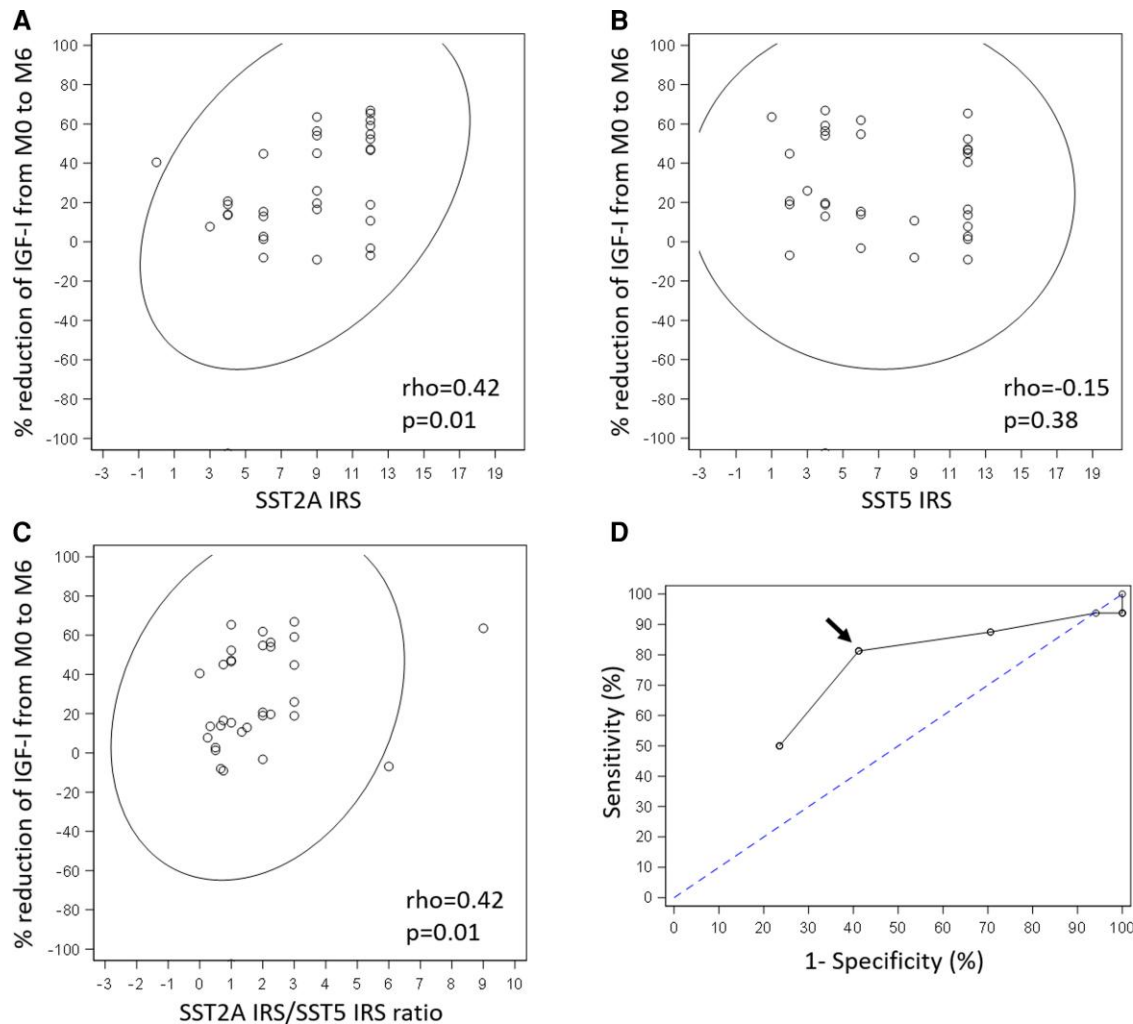


Figure 3. Octreotide LAR efficacy relative to SST2A and SST5 expression. Correlation analysis between the percent reduction of IGF-I from month 0 to month 6 under octreotide LAR and (A) SST2A IRS, (B) SST5 IRS, and (C) SST2A IRS/SST5 IRS ratio. An 95% prediction ellipse is shown. (D) ROC curve analysis that shows the best SST2A IRS cutoff (arrow) discriminating between resistant and partial responders to octreotide LAR in our cohort. Abbreviations: IRS, immunoreactive score; LAR, long-acting release; M, month; SST, somatostatin receptor.

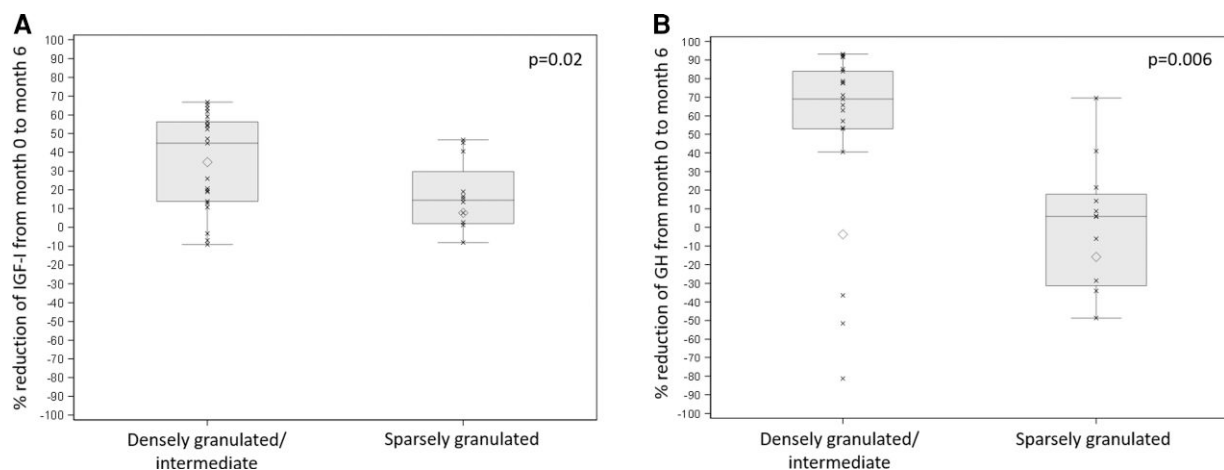


Figure 4. Association analysis between adenoma granulation pattern and the percent reduction of (A) IGF-I and (B) GH, respectively, from month 0 to month 6 under octreotide long-acting release. Individual points (crosses) and mean (rhombus) are shown.

expressed lower levels of SST5 receptor than sparsely granulated adenomas. In addition, the vast majority of sparsely granulated adenomas expressed high levels of SST5. Our group 2 was too small to allow a firm conclusion, but these sparsely granulated adenomas high in SST5 receptor might be good responders to pasireotide LAR; of note, a better response to pasireotide LAR of sparsely granulated adenomas compared with densely granulated ones have previously been noted (24). In addition, given that sparsely granulated adenomas respond less to first-generation SRLs, they may even represent a group in which pasireotide LAR would be worth trying as first-line SRL. Further studies should test whether this is the case.

Based on the T2WSI, GH-secreting adenomas can be classified as hypointense, isointense, or hyperintense. The hypointense character was associated with a better response to SRLs (mainly first-generation SRLs) both when diagnostic/baseline MRIs were used as reference for primary SRL treatment (16, 18, 42, 43) and when postoperative MRIs were used as reference for adjuvant SRL treatment (17). Conversely, a better hormonal response to pasireotide LAR administered as monotherapy or in combination with pegvisomant to patients resistant to first-generation SRL was found to be associated with hyperintense adenomas and to weakly correlate with higher baseline T2WSI (baseline here meaning when pasireotide LAR was started or maximum 1 year before) (44, 45).

In our group 1, although not statistically significant, we also found that the median percent decrease of GH was higher in hypointense than in isointense and hyperintense adenomas. However, the median percent decrease of IGF-I did not follow the same trend. This observation is different from the results of the only other study assessing the T2WSI as a predictor of response to adjuvant first-generation SRL treatment, which found at M6 a complete response in 71% of the hypointense tumors compared with in only 20% of the hyperintense tumors (17). This incongruence might be explained by the many differences between the 2 studies, including different definitions of T2WSI. That different definitions might be used to define T2WSI is important given that a recent study showed very different proportions of each signal category when using 3 different ways of defining T2WSI (the percentage of the hypointense category varied from as low as 20%

to as high as 59%) (43). We also used preoperative MRIs compared with postoperative MRIs in the aforementioned study; however, as noted in their study, no difference in T2WSI was seen between the preoperative and the postoperative MRIs (17).

The same study also found that during lanreotide Autogel treatment, 20% of adenomas shifted from 1 category of T2WSI to another (43), whereas other authors reported no change in T2WSI with first-generation SRLs (17). In our group 1, we also found that T2WSI shifted from 1 category to another between the preoperative MRI and the M6-MRI in about one-half of the patients for which the information was available. It is uncertain whether this change in T2WSI might be of biological significance, as recently proposed for the increased T2WSI seen in patients treated with pasireotide LAR (44, 45). Nevertheless, it is important to be aware of this potential change in T2WSI, especially if one wants to predict the response to more than 1 treatment (for example, to predict the response to pasireotide after first-generation SRLs). Unfortunately, our group 2 was too small to draw any conclusions, but further studies should evaluate whether the diagnostic vs the pretreatment MRI is a better predictor of response to second-line SRLs.

Of note, hyperintense adenomas were associated with a sparsely granulated pattern, whereas hypointense adenomas were associated with a densely granulated/intermediate pattern (42, 46, 47). We observed similar trends in our study. Isointense adenomas, however, were found to have an exclusively densely granulated/intermediate pattern in 1 study (42, 46) and an exclusively sparsely granulated pattern in another study (47). In our cohort, isointense adenomas were more frequently sparsely granulated. Remarkably, we found SST5 IRS to be higher in hyperintense than in hypointense adenomas. Moreover, most hyperintense adenomas presented high SST5 levels. To the best of our knowledge, we are the first to report this association between SST5 receptor expression and hyperintense adenomas. That hyperintense adenomas are more frequently sparsely granulated and with high SST5 expression, might partially explain their better response to pasireotide LAR noted in literature.

T2WSI may appear to be an interesting predictive factor of response particularly as it is noninvasive and can be used to predict response to primary SRL treatment. However, in real-

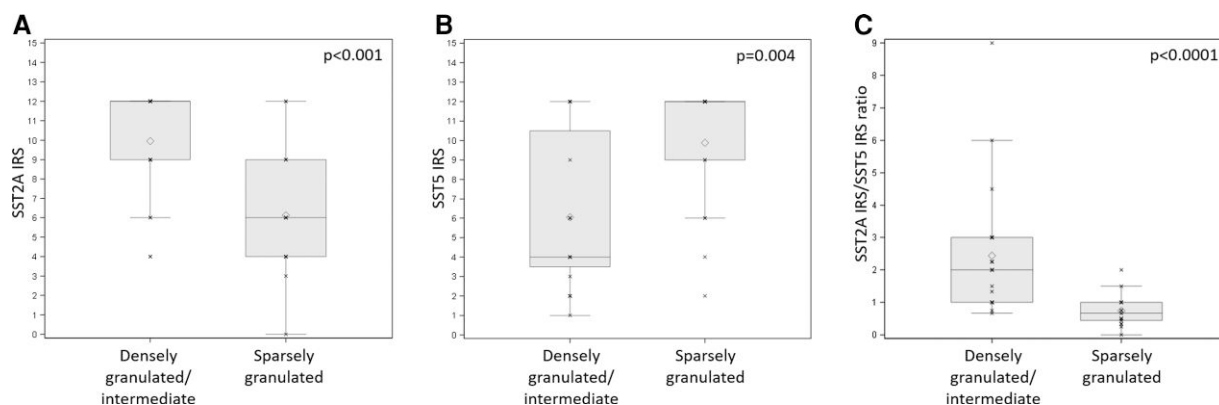


Figure 5. Association analysis between adenoma granulation pattern and somatostatin receptor (A) SST2A IRS, (B) SST5 IRS, and (C) SST2A IRS/SST5 IRS ratio. Individual points (crosses) and mean (rhombus) are shown. Abbreviations: IRS, immunoreactive score; SST, somatostatin receptor.

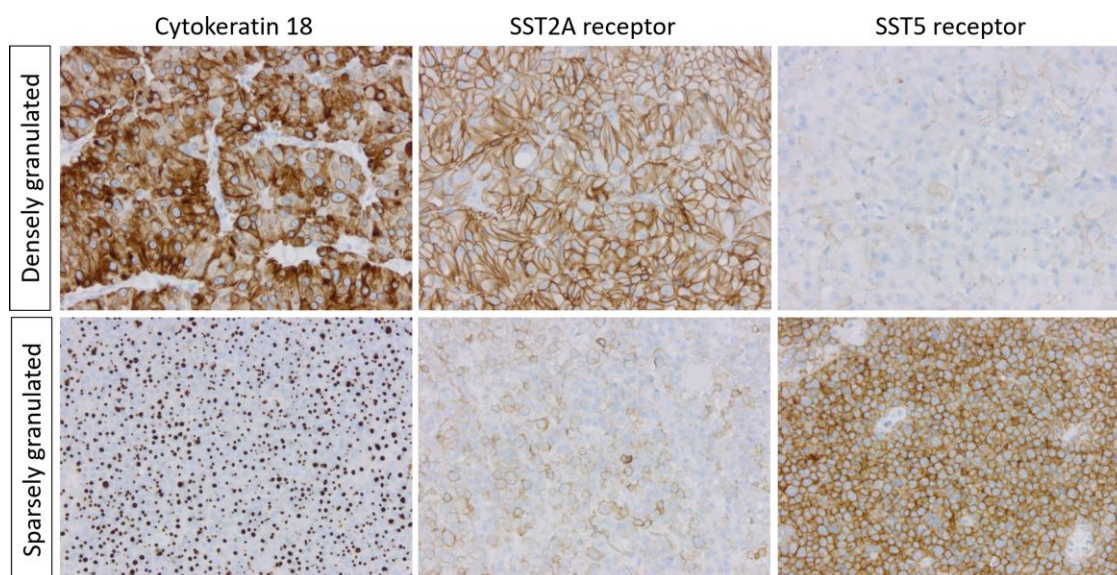


Figure 6. Examples of cytokeratin 18, somatostatin (SST)2A and SST5 receptor immunohistochemistry in a densely granulated adenoma vs a sparsely granulated adenoma (original magnification, $\times 200$), showing a diffuse cytoplasmic and perinuclear distribution of cytokeratin 18, an SST2A receptor immunoreactive score (IRS) of 12, and an SST5 receptor IRS of 2 for the densely granulated adenoma vs cytokeratin 18-positive “fibrous bodies” (dot-pattern), an SST2A receptor IRS of 4, and an SST5 receptor IRS of 12 for the sparsely granulated adenoma.

life, the MRI quality, a heterogeneous signal, or an exclusively cystic adenoma may hinder its use as a predictive factor in some cases. In our cohort, of 41 unique patients, as many as 13 patients (31.7%) had missing, uninterpretable, or heterogeneous MRIs. Others noted important numbers of heterogeneous or uninterpretable MRIs, as well, with 1 study noting that the T2WSI of 24 of 144 (16.7%) MRIs was heterogeneous (16), whereas the authors of another study noted that in their cohort of 45 patients, they were unable to use diagnostic MRIs to assess the T2WSI because of the low resolution (45). In addition, harmonization of the definitions used to define T2WSI categories would be more than welcomed to facilitate comparison between studies, but also to set a standard for the average clinician.

In conclusion, our prospective study confirms that SST2A receptor expression and adenoma granularity are good predictors of response to octreotide LAR. By contrast, we did not find that SST5 receptor expression was a good

predictor. Scoring system harmonization is needed for SST expression, and we propose the use of IRS for this. Regarding adenoma granularity, densely granulated/intermediate adenomas were more responsive to octreotide than sparsely granulated adenomas, and expressed greater levels of SST2A receptor, coupled with lower levels of SST5 receptor. The majority of sparsely granulated adenomas from our cohort expressed high levels of SST5, and this subgroup might prove to be a good responder to pasireotide LAR. When MRI is of good quality, T2WSI might be an interesting predictive factor of response, with hypointense tumors responding better to first-generation SRLs than iso- or hyperintense tumors; however, harmonization of the used definitions and optimization of MRI sequences, appear necessary. In addition, T2WSI signal can change with SRL treatment, therefore caution regarding the choice of diagnostic vs pretreatment MRI to predict response to second-line SRLs is also needed.

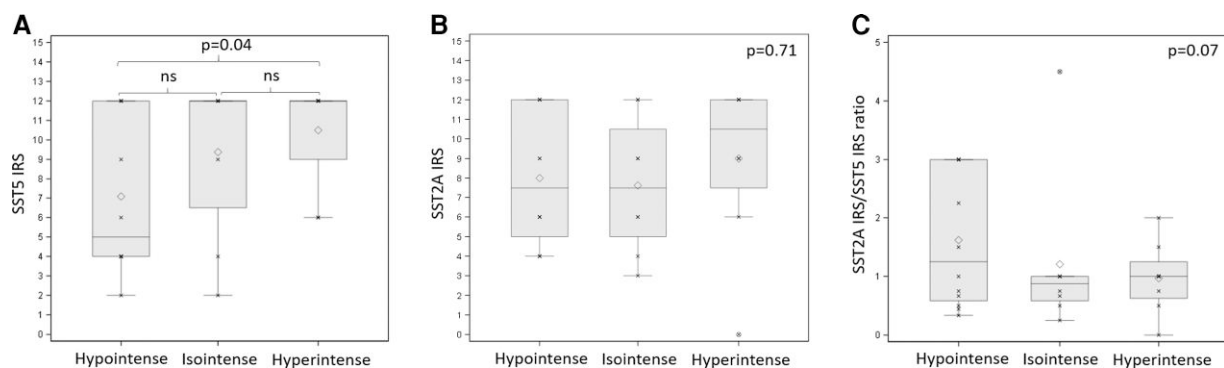


Figure 7. Association analysis between T2-weighted MRI signal intensity (evaluated on the preoperative MRI) and somatostatin receptor (A) SST5 IRS, (B) SST2A IRS, and (C) SST2A IRS/SST5 IRS ratio. Individual points (crosses) and mean (rhombus) are shown. Abbreviations: IRS, immunoreactive score; ns, nonsignificant; SST, somatostatin receptor.

Table 3. Contingency table summarizing the relationship between MRI T2 signal intensity and granulation pattern

	Hypointense	Isointense	Hyperintense	Total
Densely granulated/intermediate	9	3	3	15
Sparsely granulated	3	5	5	13
Total	12	8	8	28

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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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