Somatostatin Receptor Scintigraphy in Pituitary Adenomas: A Somatostatin Receptor Density Index Can Predict Hormonal and Tumoral Efficacy of Octreotide In Vivo

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Previous studies have failed to predict somatostatin analog response with somatostatin receptor scintigraphy in pituitary adenomas. In vitro studies have shown that the density of somatostatin receptors in pituitary tumors might be critical for octreotide response. **Methods:** The density of somatostatin receptors was calculated in vivo combining the uptake index obtained from somatostatin receptor scintigraphy and the tumor volume obtained by MRI. The ratio of these two values, called density index (DI), was established in 32 of 37 consecutive patients with pituitary adenomas (11 had growth hormone-secreting adenomas, 4 thyroid-stimulating hormone-secreting and 17 nonfunctioning). It was compared with hormonal response, assessed in 15 secreting adenomas on growth hormone or thyroid stimulating hormone suppression (which was considered significant when it reached at least 50% of basal level), and with tumor shrinkage (which was considered significant when ≥20% of pretherapeutic value) in 12 secreting and 14 nonfunctioning adenomas. **Results:** In agreement with previous reports, uptake index is not predictive of octreotide response. In contrast, DI predicts both hormonal suppression and tumor shrinkage (P = 0.009 and P = 0.0002, respectively) obtained with octreotide therapy. DI sensitivity, specificity and accuracy were 92% each, and a positive correlation was found between DI and the percentage of tumor shrinkage (r = 0.54, P = 0.004). **Conclusion:** The combination of scintigraphic and MRI data allows the computation of a DI for somatostatin receptors that points out patients who can profit from somatostatin analog treatment.

Key Words: pituitary adenomas; somatostatin receptor scintigraphy; somatostatin receptor density; octreotide efficacy

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Most secreting adenomas and approximately half of nonfunctioning pituitary adenomas express somatostatinergic receptors (SSTs), which can be detected in vitro and in vivo by somatostatin receptor scintigraphy (SRS). Somatostatin analogs are used in the management of such adenomas. It has been suggested that the differences observed in octreotide response could be related to the number of SSTs (*1,2*). Somatostatin receptor quantification was attempted using SRS uptake index or semiquantitative grading. However, discordant data have been reported concerning SRS predictive value. Therefore, in vivo estimation of the receptor density should be helpful in predicting treatment efficacy. In this study, we reviewed the data from 37 consecutive patients with pituitary adenoma who underwent SRS and then calculated an SST density index (DI). This index was defined as the ratio between the uptake index (UI = ratio of pituitary to hemispheric activities) obtained by SRS (*3*) and the tumor volume determined by MRI. This value could be calculated in 32 patients. We compared DI with hormonal response in 15 secreting adenomas (on growth hormone [GH] or thyroid-stimulating hormone [TSH] suppression) and with tumor shrinkage in 12 secreting and 14 nonfunctioning adenomas.

MATERIALS AND METHODS

Patients

Thirty-seven consecutive patients with pituitary adenoma or postoperative remnant (20 had secreting adenomas and 17 had nonfunctioning adenomas) were included in the department of nuclear medicine at Hôpital Lariboisière between October 1992 and June 1998. Patients with Cushing's disease or prolactinoma were not eligible for this study. Patients' clinical characteristics at the time of scintigraphy are given (Table 1).

Fourteen patients had GH-secreting adenomas (A1–A14). Five had undergone surgery, and none had undergone radiotherapy. At the time of scintigraphic study, all patients had active acromegaly with elevated plasma GH, nonsuppressible by an oral charge of glucose, and had elevated insulin-like growth factor-1 (IGF1) levels. Three (A2, A7 and A10) had visual field defects.

Six patients had TSH-secreting adenomas (T1–T6), according to the following criteria: preoperative inappropriate plasma TSH levels with high plasma free T4 or free T3 and radiological

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TABLE 1
Patient Characteristics

Patient no.	Sex	Age	Previous therapy	Volume index (cm^3)	Uptake index	Density index	Treatment		Hormonal decrease (%)	Tumor volume shrinkage (%)
							Dose (μg/d)	Duration	GH	
A1	M	44	None	0.8	2.7	3.38	AC		−97	NA
A2	M	30	None	2.5	3.4	1.36	300	3 mo	−52	−21
A3*	M	47	None	2.9	2.1	0.72	300	1 mo	−89	−62
A4	M	51	None	2.5	1.7	0.68	300	1 mo	−51	−26
A5*	M	35	None	4.9	2.8	0.57	300	3 mo	−92	−35
A6	M	34	None	3.1	1.7	0.55	AC		−84	NA
A7*	F	78	None	5.2	2.7	0.52	300	3 mo	−89	−24
A8	F	27	D	8.4	2.7	0.32	300	2 mo	−37	−40
A9	F	38	D S	9.6	3.0	0.31	300	9 mo	−93	−66
A10	F	19	S	13.5	2.7	0.2	300	6 mo	0	0
A11	F	64	S	17.4	2.8	0.16	300	6 mo	−18	+15
A12*	F	53	D	UD	1.6	NA	300	2 mo	−48	NA
A13	F	53	S	NDR	1.5	NA	300	1 mo	−77	NA
A14*	F	37	S	UD	1.4	NA	300	3 mo	−32	NA
									TSH/α subunit	
T1	F	43	None	0.6	2.1	3.5	AC		−89/NA	NA
T2	F	40	S	2.5	2.1	0.84	300	3 mo	−92/−92	−25
T3	M	57	None	13.4	4.8	0.36	300	3 mo	−67/−74	−23
T4	F	47	S	6.5	2.3	0.35	300	1 mo	0/−29	−45
T5	M	73	S R	UD	3.1	NA	AC		−44/−71	NA
T6	F	27	S	NDR	2.9		AC		−55/−20	NA
N1	M	41	S	2.9	4.3	1.48	300	3 mo		−61
N2*	F	37	S	13.9	15.1	1.09	300	9 mo		−36
N3*	F	38	None	10.4	3.7	0.36	150	1 mo		+13
N4	F	67	S	7.7	2.2	0.29	300	1 mo		0
N5	F	51	S	13.8	3.6	0.26	300	1 mo		0
N6*	F	32	S D	9.7	2.2	0.23	300	6 mo		−11
N7	M	63	S	15.8	2.9	0.18	300	1 mo		0
N8	F	56	D	20	2.8	0.14	300	1 mo		0
N9	M	36	None	31	3	0.1	300	1 mo		−31
N10	M	58	None	22.5	2	0.09	300	1 mo		−3
N11	M	80	None	24.8	1.8	0.07	300	1 mo		+7
N12*	M	40	None	28.8	1.7	0.07	300	5 d		NA
N13*	F	60	None	25	1.6	0.06	300	2 d		NA
N14*	F	74	S R	72.8	3.7	0.05	300	1 mo		0
N15*	F	61	S R D	54.4	2.2	0.04	300	6 mo		−14
N16*	M	68	None	145	2.5	0.02	300	9 mo		−16
N17	F	70	None	126	1.7	0.01	300	2 d		NA

*Some data from these patients appear elsewhere (*3,27*).

GH = growth hormone; AC = acute test (100 μg intravenous); NA = not available; D = dopamine agonists; S = surgery; UD = unwell delineated; NDR = no detectable remnant; TSH = thyroid-stimulating hormone; R = radiotherapy.

evidence of adenoma on MRI. Moreover, confirmation was obtained by immunohistochemistry (IHC) staining in every case. At the time of scintigraphy, 4 patients had been operated on and 1 (T5) had adjunctive radiotherapy 6 y before. All 6 had persistent, inappropriate TSH secretion when entering the study. Two of them (T3 and T4) had visual defects.

Seventeen patients had nonfunctioning macroadenomas (N1–N17) detected by MRI and confirmed by IHC in 15 patients. In 2 (N15 and N16), diagnosis was made on the evidence of intrasellar tumor and elevation of plasma free α-subunit levels. At the time of scintigraphy, 8 had been operated on and 2 had undergone radiotherapy 25 (N15) and 30 y earlier (N14). All but 3 patients (N1, N4 and N15) had visual defects. Data from some patients appear in Table 1.

Hormone determinations: Using commercially available kits, serum GH, IGF1, free thyroxine and tri-iodothyronine hormones, follicle-stimulating hormone and luteinizing hormone were assayed by radioimmunoassay, free α-subunit by immunoradiometric assay and TSH by chemiluminescence.

IHC was performed as reported previously (*4*). Immunospecific staining was considered positive when at least 10% of tumor cells were stained with the corresponding antibodies.

Visual fields were studied using the Goldmann perimeter method before and during treatment.

Tumor volume index was calculated as the product of the three largest diameters (transverse, vertical and anteroposterior) obtained from contiguous 3-mm sections of computerized sagittal and coronal slices on MRI, before and after treatment as previously described (*4*). All data were read by two independent observers, and interobserver reproducibility was determined. The retained value was the average of values determined by each observer.

SRS was performed as described previously (*3*): 111 MBq ^{111}In-pentetreotide were given as an intravenous bolus injection. Lateral planar images were obtained 24 h after injection with a double-head, large-field-of-view gamma camera (DHD Sopha Medical, Buc, France) fitted with medium-energy, parallel-hole collimators. The photopeak was centered over 173 keV with a window width of 20%. Digital images were recorded with a Sophy computer (Sopha Medical). Acquisition parameters were as follows: 128 × 128 word matrix, 10 min/view. An uptake index was then calculated: a circular region of interest (ROI) was visually positioned over the pituitary and the size of this ROI was adjusted to best fit the pituitary gland. Then this ROI was copied to generate five identical ROIs, positioned over the hemispheric area. UI was determined as the ratio of the pituitary adenoma to the mean activity of the five hemispheric areas (i.e., background). Data were read by two independent observers, and reproducibility was determined. SST DI was expressed as the ratio of UI to the basal tumor volume (Vb), obtained before octreotide treatment as stated above.

Octreotide treatment (300 μg/d) was given after scintigraphy for 1 mo or more in most patients (Table 1). However, 3 patients (N12, N13 and N17) had visual deterioration within a few days and underwent surgery, 1 received only 150 μg/d for 1 mo (N3) and 5 patients with secreting adenomas had a single 100-μg dose (A1, A6, T1, T5 and T6).

Hormonal octreotide effect was assessed in all patients with secreting adenoma, comparing hormonal levels (GH for acromegalics, TSH and α-subunit for thyreotropic adenomas) before and during treatment as follows: baseline hormonal levels were expressed as the mean of blood samples obtained hourly between 8 AM and 4 PM, therapeutic levels were expressed as the mean of blood samples obtained hourly between 8 AM and 4 PM for long-term treatment patients and as the nadir levels in the 5 patients who received a single dose.

Octreotide efficacy was defined as tumor reduction of at least 20% (*5–8*) or hormonal suppression of at least 50% of baseline levels (*6,9,10*).

Result Analysis

Quantitative results were expressed as median and range. Vb, UI and DI, measured before treatment, were compared according to (a) adenoma characteristics (secreting or nonfunctioning), (b) hormonal response in patients with secreting adenomas and (c) tumor shrinkage in all patients. Association between quantitative data was performed by linear correlation and comparisons of variables between groups was performed with nonparametric Mann-Whitney U test. $P < 0.05$ was considered significant. Sensitivities and specificities of DI and Vb were determined by multiple iterations, using threshold values ranging from 0.15 to 0.6 for DI (with steps of 0.05) and from 1 to 30 for Vb (with steps of 1).

RESULTS

Pretreatment Pituitary Imaging Data

SRS acquisitions allowed the delineation of the contours of every adenoma, even in cases of low uptake (n = 9). For UI, interobserver variability was <5%, as previously reported (*3*). Tumor volume at the time of MRI (Table 1) could be calculated in 32 of 37 patients with a good interobserver reproducibility ($r = 0.99$, $P < 0.001$). Pretreatment tumor volume (Vb) and SRS parameters (UI and DI) are shown (Table 1). For UI, there was no significant difference between secreting and nonfunctioning tumors (Table 2). Conversely, Vb was significantly greater for nonfunctioning adenomas than for secreting adenomas ($P = 0.008$), and DI was significantly higher for secreting adenomas ($P = 0.01$) (Table 2).

Octreotide Efficacy

Tumor volume was followed up in 26 of the 32 patients with available Vb determination (Table 1) because 3 had a single dose test of octreotide (A1, A6 and T1) and 3 others underwent surgery within a few days because of octreotide failure shown by visual deterioration (N12, N13 and N17). Interobserver reproducibility was $r = 0.92$ ($P < 0.001$) for tumor shrinkage measurement. Thirteen of these 26 patients with tumor follow-up had tumor shrinkage (Table 1): 10 of the 12 patients with secreting (A: 7/9; T: 3/3) and 3 of the 14 with nonfunctioning adenomas. Simultaneous visual normalization occurred in 3 patients with secreting adenomas (A3, A7 and T3) and in 1 with nonfunctioning adenoma (N2); partial improvement appeared in patient N9. In addition, 1 patient (N7) with no detectable tumor shrinkage had visual improvement.

Fifteen of the 20 patients with secreting adenomas had hormonal suppression (Table 1): 10 of the 14 acromegalics (71%) and 5 of the 6 patients with TSH-secreting adenoma. It is worth noting that tumor shrinkage occurred without hormone suppression in 2 patients (A8 and T4).

Relationship Between Imaging Indices and Octreotide Efficacy

The relationship between imaging indices and octreotide efficacy is shown in Table 3. UI was similar in patients with or without tumor shrinkage. DI was significantly higher

TABLE 2
Imaging Quantitative Data Before Octreotide Treatment

Index	Secreting adenomas	Nonfunctioning adenomas
Vb (cm^3)		
Median	4.90	22.50*
Range	0.6–17.4	2.90–145
UI		
Median	2.70 NS	2.50 NS
Range	1.40–4.80	1.60–15.10
DI		
Median	0.55	0.09†
Range	0.16–3.50	0.013–1.48

*$P < 0.05$.
†$P < 0.01$.
Vb = basal tumor volume index; UI = uptake index; NS = not significant; DI = somatostatin receptor density index.

TABLE 3
Imaging Quantitative Data According to Octreotide Responses

Index	Hormonal response		Tumor volume response	
	≥50%	<50%	≥20%	<20%
Vb (cm^3)				
Median	2.9	10.95*	5.2	17.4†
Range	0.6–13.4	6.5–17.1	2.5–31	7.7–145
UI				
Median	2.7	2.7 NS	2.8	2.7 NS
Range	1.5–4.8	1.4–2.8	1.7–15.1	1.8–3.7
DI				
Median	0.68	0.26†	0.57	0.16†
Range	0.31–3.50	0.16–0.35	0.97–1.48	0.02–0.35

*$P < 0.05$.
†$P < 0.01$.
Vb = basal tumor volume index; UI = uptake index; NS = not significant; DI = somatostatin receptor density index.

($P = 0.0002$) and Vb significantly smaller ($P = 0.0009$) in patients whose tumor shrank. Moreover, a positive correlation was found between DI and the percentage of tumor shrinkage ($r = 0.54$, $P = 0.004$). Threshold values for optimal sensitivities and specificities were 0.3 for DI and 10 for Vb and the corresponding sensitivities, and specificities were both 92% for DI and 77% and 85%, respectively, for Vb; accuracy was 92% for DI and 81% for Vb.

As far as hormonal response was concerned, UI showed no difference between responsive and unresponsive cases, and we found no correlation between UI and the percentage of GH reduction. Conversely, DI was significantly higher ($P = 0.009$) in patients with hormone suppression who also had lower Vb ($P = 0.02$). We found a negative correlation between Vb and the percentage of GH suppression during octreotide treatment ($r = -0.69$, $P = 0.02$).

DISCUSSION

As soon as octreotide was available for therapeutic use, the prediction of its efficacy was questioned. In acromegaly, GH suppression by the first dose of octreotide was shown to be predictive of its long-term efficacy on hormonal secretion (*11–13*). This is not the same for TSH-secreting adenomas, which usually respond gradually (*14*). Secretion control does not predict tumor shrinkage (*6,15,16*). For nonfunctioning adenomas, the only assessed criteria of treatment efficacy are visual defect and adenoma volume follow-up. Long-term treatment was proposed only for patients who experienced early vision improvement (*8*).

The usefulness of scintigraphic imaging in predicting octreotide efficacy was then studied. Quantitative UI or a semiquantitative grading of tracer fixation was reported to fail in predicting tumor shrinkage in previous studies (*17–19*) as in this study. In this study, the percentage of adenomas that shrank is similar to other studies of acromegalics (*6,7,20*) and thyreotropic adenomas (*14*). The poor proportion of nonfunctioning adenoma responders in this study is also in agreement with other studies (*6,19,21,22*).

As far as hormonal response is concerned, we obtained similar suppression compared with other studies of acromegaly (*10,19,23,24*) and thyreotropic adenomas (*14,25,26*). However, we were not able to confirm the significant relationship between UI and the percentage of GH suppression observed previously (*27*) in our subset of 14 acromegalics. This discrepancy was observed in other studies, some suggesting a fair predictive value of SRS fixation for hormonal octreotide efficacy (*10,28–30*), others reporting negative results (*19,31*).

In a previous multicentric study we participated in (*27*), an approach of in vivo SST density (determined as the ratio of UI to the maximal vertical diameter) was obtained and was significantly lower in nonfunctioning than in secreting adenomas. However, this relative index was not validated with respect to octreotide efficacy, but this previous study was not designed to address this point. Therefore, the calculation of the adenoma volume (which is directly used in our SST DI) has been improved, taking into account the three largest diameters (i.e., transverse × vertical × anteroposterior), instead of only one, to better fit the true volume. This new index (DI) was also significantly lower in nonfunctioning adenomas than in secreting tumors ($P = 0.01$) but provides additional information compared with a UI alone. Compared with UI, DI was significantly higher in patients with hormonal suppression ($P = 0.009$) and with tumor shrinkage ($P = 0.0002$), with a sensitivity and specificity of 92% and an accuracy of 92%. Moreover, we found a positive correlation between DI and the percentage of tumor shrinkage ($r = 0.54$, $P = 0.004$). If hormonal reduction can be predicted by an acute octreotide test in most secreting adenomas, no test was reported as predicting tumor shrinkage in either secreting or nonfunctioning adenomas. In this study, the additional value of SRS over MRI alone in patient management would be to spare treatment in 1 patient and to avoid surgery in another (N2) whose visual abnormalities normalized during octreotide treatment.

For this purpose, DI seems clinically relevant for somatostatin analog treatment of patients presenting with a pituitary adenoma even if further studies are useful to confirm these preliminary results.

CONCLUSION

This study shows that the combination of scintigraphic and MRI data allows DI SST to be computed, which indicates patients who could benefit from somatostatin analog treatment.

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