Long-Term Octreotide Therapy in Growth Hormone–Secreting Pituitary Adenomas: Evaluation with Serial MR

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PURPOSE: To compare the changes in tumor volume with length of octreotide treatment in patients with acromegaly, to analyze signal alterations of the pituitary mass during treatment, and to determine an optimal MR imaging protocol. **METHODS:** Eighteen patients with growth hormone (GH)-secreting pituitary adenomas were studied with MR imaging before and during octreotide treatment. The length of follow-up was 9 to 70 months. Tumor volume, extension, and signal characteristics were evaluated. **RESULTS:** The total pituitary volume decreased in 16 patients by a mean of 37%. In 11 patients the tumor could be demarcated from the normal gland, and mean tumor reduction was 51%. Most of the tumor reduction took place within the first year, but an additional effect was noted in four patients during the following 3 years. Tumor reexpansion, hemorrhage, or necrosis did not occur. Serum GH levels were effectively lowered within the first year, with slight additional reductions thereafter. **CONCLUSION:** In long-term octreotide treatment of GH-secreting pituitary adenomas, tumor shrinkage occurs primarily during the first year, but effects are noted up to 4 years. The treatment may be considered an alternative to surgery in the select group of patients in whom the peripheral effects of chronic GH elevation, as determined by serum insulinlike growth factor I (IGF-I), are controlled. We suggest MR imaging with T1-weighted coronal and sagittal images at baseline and after 3 and 12 months, with additional MR imaging if GH or IGF-I levels rise during treatment. At baseline, both noncontrast and contrast-enhanced images should be obtained. Unenhanced images may be sufficient during follow-up unless tumor reexpansion occurs or surgery is anticipated.

Index terms: Adenoma; Chemotherapy; Pituitary gland, neoplasms

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In patients with acromegaly, complete removal of a pituitary growth hormone (GH)-secreting tumor by transsphenoidal surgery is the treatment of choice. However, in 20% to 50% of the cases radical surgery is not achieved because of invasive growth or large tumor extension (1). These patients need additional treatment, such as radiation therapy or medication. The long-acting somatostatin analogue octreotide (SMS 201–995) has been found to be effective in reducing serum levels of GH and insulinlike growth factor I (IGF-I) (2, 3), but little attention has been paid its long-term effects on tumor size. In earlier studies it has been found that treatment with octreotide during a period of approximately 6 months is associated with tumor reduction in about one fifth to one half of the patients as assessed by computed tomography (CT) (4–10). Compared with CT, magnetic resonance (MR) imaging offers several advantages in the assessment of pituitary adenomas (11–13). Apart from allowing better demarcation of the tumor from normal pituitary gland and the surrounding structures, MR imaging also provides information on intratumoral events, such as necrosis and hemorrhage (13).

A prolonged follow-up period is of great clinical interest, since this will give information on the effect of octreotide therapy with respect to tumor growth and provide a basis for future

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Patient data, length of follow-up, serum GH levels (S-GH), total pituitary and tumor volume, and tumor extension

Patient	Age, y/Sex	Length of Follow-up, mo	Initial S-GH, μg/L	Reduction of S-GH, %	Initial Total Pituitary Volume, cm^3	Reduction of Pituitary Volume, %	Initial Tumor Volume, cm^3	Reduction of Tumor Volume, %	Pituitary Volume Reduction		Initial Tumor Extension	
									First Examination to Show, mo	Last Examination to Show, mo	Supra-sellar	Invasive
1	49/F	22	11.0	87	0.5	0	0.1	0	. . .	. . .	No	No
2	43/F	28	12.2	86	0.8	25	0.1	0	11	11	No	No
3	50/F	13	21.5	79	0.8	38	0.1	50	7	13	No	No
4	52/M	49	15.6	90	0.8	25	0.3	NC	49	49	No	No
5	46/F	60	26.2	95	1.0	40	0.8	50	6	6	No	CS
6	60/M	70	9.5	90	1.1	45	0.5	60	24	24	No	No
7	56/F	23	20.3	86	1.3	38	0.4	NC	6	6	No	No
8	45/M	28	26.0	81	1.4	43	0.8	50	6	6	No	No
9	67/F	49	45.4	91	1.4	50	1.2	67	8	37	No	No
10	59/F	17	35.5	91	1.6	25	1.4	43	5	5	No	No
11	64/F	61	30.8	88	1.8	33	1.4	64	7	7	No	CS
12	70/F	12	10.0	76	1.9	37	NC	NC	6	12	No	No
13	42/M	65	19.9	97	2.1	29	1.9	26	12	12	No	Sph S
14	45/F	12	15.7	69	2.1	43	NC	NC	4	4	No	No
15	61/M	46	43.1	89	3.4	18	NC	NC	13	13	No	Sph S
16	31/M	19	50.5	88	3.6	36	NC	NC	10	16	Yes	CS
17	48/F	9	124.7	66	3.7	0	2.6	0	. . .	. . .	No	Sph S
18	22/F	21	74.8	93	5.6	71	5.0	NC	5	21	Yes	CS

Note.—The patients are ordered according to increasing initial total pituitary volume. NC indicates not calculated, the tumor could not be separated from the normal pituitary tissue; underlines indicate first examination after start of therapy; CS, cavernous sinus; and Sph S, sphenoidal sinus.

neuroradiologic monitoring of GH-secreting adenomas in patients selected for this treatment. This study was designed to evaluate changes in tumor volume with octreotide treatment, to analyze the signal of the pituitary mass during treatment, and to determine the proper MR imaging protocols.

Patients and Methods

Eighteen patients, 12 women and six men (mean age, 51 years), with GH-secreting pituitary adenomas were studied prospectively (Table). They constituted a consecutive series referred to the department of medicine during a 4-year period. Informed consent was obtained in all cases.

The diagnosis was established clinically, radiologically, and biochemically (elevated GH and IGF-I concentrations and nonsuppressibility of serum GH below 2 μg/L after oral glucose administration), and was verified histopathologically in 13 patients after transsphenoidal surgery (n = 12) or frontolateral craniotomy (n = 1). The initial serum GH concentration ranged from 9.5 to 125 μg/L (Table). Seventeen patients had not been treated previously. One patient (case 13), with a large recurrent tumor, had undergone surgery and radiotherapy several years earlier and had also been treated with bromocriptine. Two patients had slightly elevated serum prolactin (PRL) levels (<50 μg/L) thought to be due to compression of the pituitary stalk; there were no signs of mixed GH/PRL activity.

Octreotide (Sandostatin, Sandoz Ltd; Basel, Switzerland) was administered in divided doses by subcutaneous injections two to three times daily, with total doses ranging from 200 to 2500 μg (median dose, 300 μg). Serum GH was determined by a radioimmunoassay using polyclonal antibodies (14). The mean GH level was calculated from samples obtained on nine separate occasions over a 24-hour period. IGF-I in serum was measured by an immunoradiometric assay after formic acid-ethanol extraction (Nichols Institute Diagnostics; San Juan Capistrano, Calif). In total, 71 MR studies and nine CT examinations were performed, the latter in four patients (partly because of claustrophobia). In all patients an examination was carried out within 5 months (within 2 months in 16 patients) before treatment. The duration of follow-up varied from 9 to 70 months (mean, 34 months). After the start of therapy, examinations were performed at approximately 2 (n = 5), 6 (n = 12), 9 (n = 3), 12 (n = 14), 18 (n = 3), 24 (n = 11), 36 (n = 5), 48 (n = 5), and 60 to 70 (n = 4) months. The number of imaging studies in the same patient varied from three to six.

Fifty-two MR studies were acquired on a 0.5-T superconductive unit. Sagittal and coronal T1-weighted spin-echo images were obtained with parameters of 500/30/2 (repetition time/echo time/excitations); coronal proton density– and T2-weighted dual-echo images were obtained with parameters of 1500–2000/30,90–120/1–2 and a section thickness of 5 mm. In 18 of these 52 examinations, coronal T1-weighted images were also obtained after intravenous administration of gadopentetate dime-

glumine (0.1 mmol/kg). Fourteen MR studies were acquired on another 0.5-T superconductive unit. Sagittal T1-weighted images were obtained with parameters of 450–520/13–20/2–4 and a section thickness of 3 to 5 mm. A coronal three-dimensional fast field-echo acquisition was obtained with parameters of 30/13/2–4, a flip angle of 30°, and a section thickness of 1.5 to 2.7 mm. The latter was repeated after administration of contrast material. Five studies were carried out with a 1.0-T superconductive unit; 3-mm coronal and sagittal T1-weighted images (500/15–17/2–4) were obtained before and after administration of contrast material.

All images were evaluated in a nonblinded manner by one neuroradiologist. The total pituitary diameters were measured on the hard-copy sagittal and coronal MR images or on the coronal CT scans. The sagittal, transverse, and vertical maximum diameters covering both the tumor and the residual pituitary tissue were recorded; on CT scans the sagittal diameter was estimated from the number of sections covering the sellar contents. The total pituitary volume was estimated as the product of these diameters × 0.5 (15, 16). A reduction by 18% of the original volume was considered to be significant (16). If the tumor could be demarcated from the normal pituitary gland, a corresponding tumor volume was calculated. An enhancing area, crescent-shaped or resembling a normal pituitary gland, was regarded as probable residual pituitary tissue (17).

The evaluation included the tumor extension and its relationship to the optic chiasm, the cavernous sinus, and the base of the skull. Cavernous sinus invasion was considered to be present when the internal carotid artery was encased by the tumor (18).

Signal intensity was evaluated visually. Signal intensity similar to that of cerebral gray matter was considered to represent solid tissue. Nonenhancing areas and/or high signal intensity on the T2-weighted image with low or intermediate intensity on the corresponding T1-weighted image was considered to represent necrosis or cysts (19).

The results were analyzed statistically with Wilcoxon's signed rank test and with linear regression. Probabilities below .05 were accepted as indicating significance.

Results

Growth Hormone Levels

The findings are summarized in the Table. All subjects initially had elevated levels of growth hormone, which during octreotide therapy were lowered by an average of 60% after 2 months and by an average of 85% after 2 years of treatment. Subsequently, further minor reductions occurred (Fig 1). In 12 patients, a mean 24-hour GH level of less than 5 μg/L was noted during long-term treatment, and in five of these patients serum IGF-I levels within the age-appropriate reference limits were achieved (100 to 340 μg/L). Before therapy, the total pituitary volume was positively correlated with the serum GH level ($r = .73$, $P = .006$), and inversely correlated with the age of the patients ($r = .51$, $P < .03$).

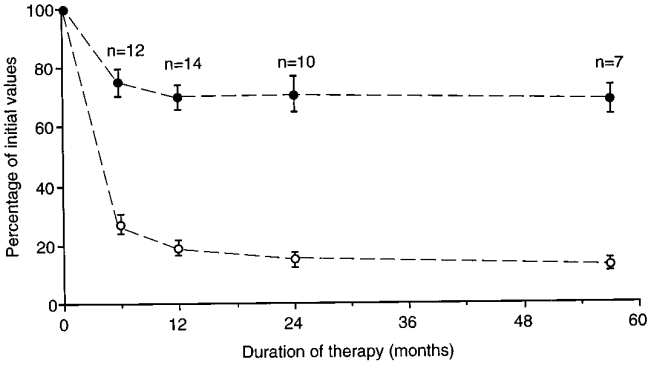

Fig 1. The effects of octreotide on the total pituitary volume (*closed circles*) and serum GH levels (*open circles*) during long-term treatment of 18 patients with acromegaly, expressed as percentages of the pretreatment values (mean ± SEM). The data shown at 57 months represent observations within the interval of 48 to 70 months.

Tumor Size and Tumor Extension

In 16 patients the total pituitary volume decreased during therapy. In 10 of these patients a significant reduction was noted at 4 to 8 months, in four patients at 1 year, in one patient at 2 years, and in one patient at 4 years (Table). In 13 of the 16 patients these examinations were the first to be performed after the initiation of therapy, and the shrinkage could therefore have occurred earlier. Thereafter, a further reduction was noted in five patients (Table; Fig 2). Most of the reduction took place during the first year: the mean residual pituitary volume at 6 months was 75% of the initial volume, and at 1, 2, and 4 to 6 years it was 71%, 70%, and 68%, respectively (Fig 1). In four patients a reduction was noted after the first year, and the latest reduction occurred after 49 months of therapy. In the latter patient (case 4) there was a slight gradual decrease, which was significant only at 49 months. The maximum reduction ranged from 18% to 71% (mean, 37%). The shrinkage of the pituitary volume did not correlate with the suppression of GH secretion or with the initial tumor size.

The tumor volume could be determined both before and during therapy in 11 patients. In eight of these the tumor volume decreased (Ta-

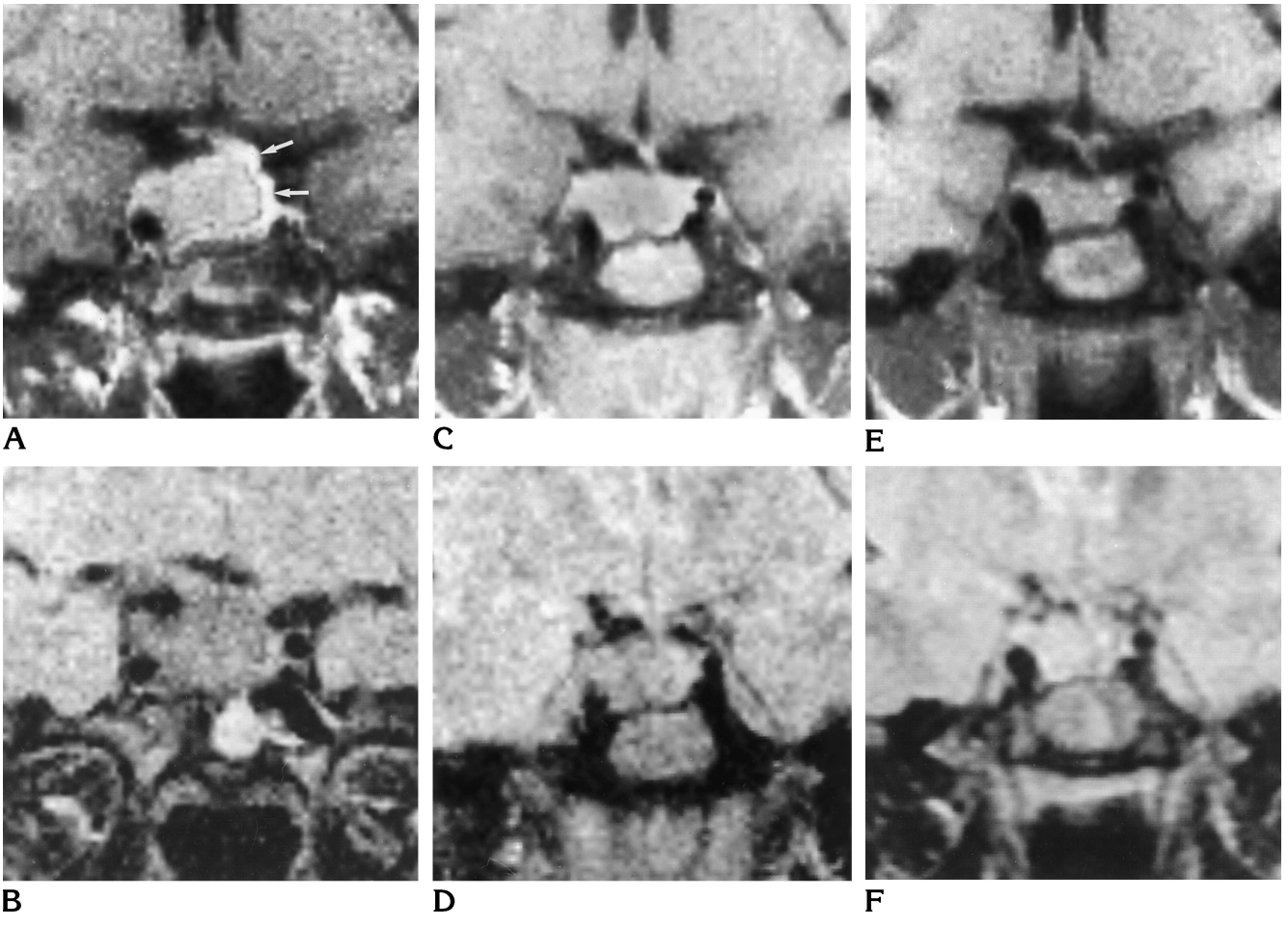

Fig 2. Patient 18.

Before therapy, contrast-enhanced coronal T1-weighted MR image (500/30) (*A*) and coronal T2-weighted image (1500/90) 5 mm more anteriorly (*B*) show that the tumor has invaded the right cavernous sinus and compressed normal pituitary tissue (*arrows, A*), which is visible to the left of the tumor. The tumor extends superiorly but the chiasm is not displaced. It appears hypointense on the T2-weighted image.

Five months after initiation of therapy, contrast-enhanced coronal T1-weighted MR image (*C*) and coronal T2-weighted image (1800/90) (*D*) show that the tumor has decreased in size and the suprasellar part has disappeared. The tumor remains slightly hypointense on the T2-weighted image.

E and *F*, Unenhanced coronal T1- and T2-weighted MR images, respectively, at 1 year show further size reduction. The tumor now appears isointense on the T2-weighted image.

ble; Fig 3), in general by more than the total pituitary volume, with the reduction ranging from 26% to 67% (mean, 51%). In one patient with a microadenoma there was no definite decrease in tumor size although the total pituitary volume was reduced.

Both the total pituitary volume and the tumor volume were significantly diminished at 6 months ($P = .003$ and .03, respectively), and for the total pituitary volume the significance was stronger at 1 year.

In two patients (cases 1 and 17) there was no significant change either in the total pituitary volume or in the tumor volume during therapy, even though the GH levels decreased by 87% and 66%, respectively. In one patient octreotide was discontinued after 2 years of therapy. MR imaging performed 1 month later showed slight reexpansion of the tumor (Fig 4). No other case of tumor expansion was noted.

Four tumors were microadenomas and 14 were macroadenomas. Eleven tumors were only located intrasellarly and two had a suprasellar component without compression of the chiasm; in both cases the suprasellar part of the tumor disappeared completely during therapy (Fig 2). Seven tumors showed invasion into the cavernous sinus or the sphenoidal sinus. The

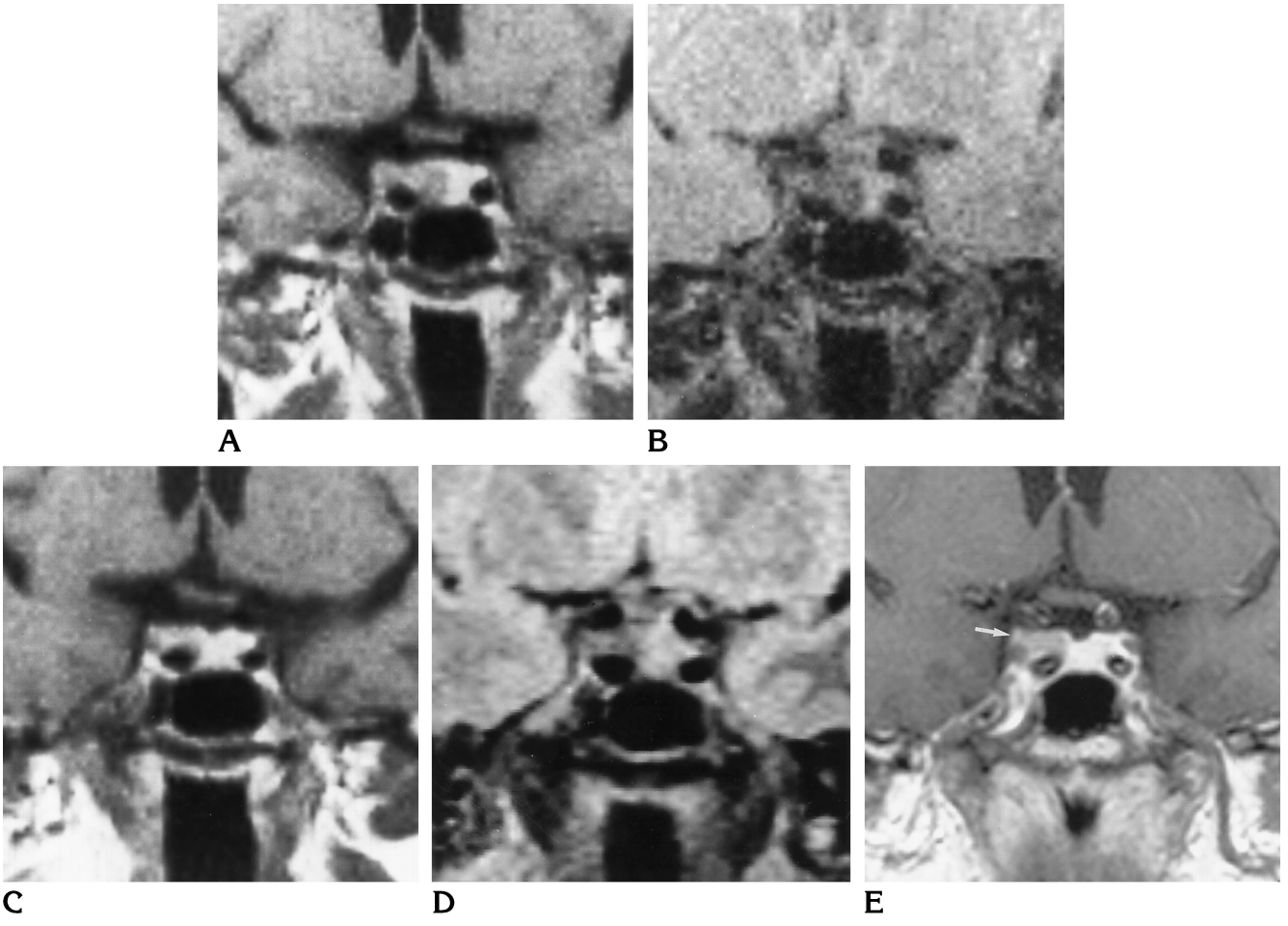

Fig 3. Patient 11.

Before therapy, contrast-enhanced coronal T1-weighted image (500/30) (*A*) and corresponding T2-weighted image (1500/90) (*B*) show the tumor is located within the sella and in the right cavernous sinus. It is hypointense on the T2-weighted image (from Lundin et al [32]).

Seven months after initiation of therapy, contrast-enhanced coronal T1-weighted image (*C*) and corresponding T2-weighted image (1800/90) (*D*) show the tumor has decreased in size by 60% and the total pituitary volume (including the right cavernous sinus area) has decreased by 29%. Remaining hypointensity is seen on the T2-weighted image.

E, At 61 months, contrast-enhanced coronal T1-weighted image (500/15) shows no additional significant change in the tumor volume; an apparent increase is thought to be due to better technical quality. The tumor still extends into the right cavernous sinus (*arrow*).

invasive tumor components decreased in size in parallel with the overall size reduction.

Signal Intensity Analysis

In one patient an area with the appearance of a cyst or necrosis was found before therapy. At 5 months this area was slightly larger, and the tumor size smaller. There were no signs of cysts, necrosis, or hemorrhage in any of the other tumors. Visually, the tumors were approximately isointense with gray matter on T1- and proton density–weighted images, both before and during therapy. On T2-weighted images five tumors were isointense and 10 were hypointense; three of the latter changed to isointense after 6 to 24 months (Fig 2). On contrast-enhanced images, the tumors were hypointense compared with the normal gland; this did not change during therapy.

Discussion

In this study of 18 patients with GH-secreting pituitary adenomas, only one of whom had received previous therapy, we established that long-term treatment with octreotide is effective in reducing both the GH levels and the tumor

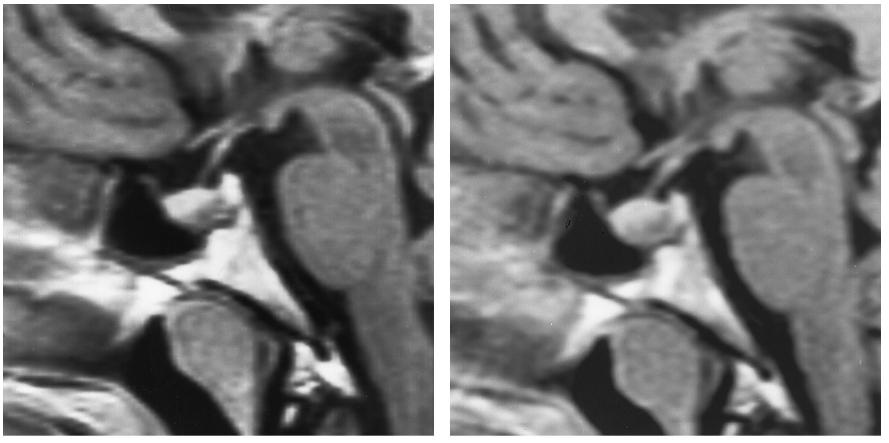

Fig 4. Patient 7.

Contrast-enhanced sagittal T1-weighted images (520/20). At 14 months (*A*), residual microadenoma is seen in the lower part of the sella; the total pituitary volume has decreased by 38% in comparison with the original volume. At 23 months (*B*), octreotide was discontinued for 1 month. The tumor is now larger and the pituitary volume has increased by 30%, with more pronounced convex bulging of the upper surface.

volume. The effect was gradual. Most of the shrinkage was evident within 6 months, after which small additional effects were noted up to 49 months of treatment. With the use of serial MR imaging we could closely follow the changes in tumor size and analyze the signal characteristics of the tumors. The duration of follow-up was longer than in previous studies (4–10, 20–22), and this provided a new perspective on the effects of octreotide on GH-secreting adenomas.

On a short-term basis, our findings are in agreement with those reported previously in which the duration of follow-up was shorter and the evaluation made with CT (6, 20–22) or MR imaging (7, 9). Extending the duration of treatment to up to 6 years, we found tumor shrinkage in a higher proportion of patients than in most other investigations. With a treatment period of 1.5 to 7 months, the proportion of patients responding with tumor shrinkage has ranged from 19% to 60% (7, 9, 20), but in one study all tumors decreased in size (21). The major shrinkage has been noted within 1 to 2 weeks (9, 20) or after 8 to 12 weeks (21), with minor additional shrinkage in a few patients (9, 21). A gradual decrease in sellar volume over 18 to 19 months has been found, however, in two studies that used CT (6, 22). In two studies, tumor shrinkage was directly related to pretreatment tumor volume, indicating a better response in larger tumors (7, 9).

In rare cases, an impressive shrinkage of GH-secreting tumors has been reported (23–25). In one case, the tumor recurred once octreotide was discontinued (24). In another patient, who had mixed GH and prolactin secretion and who was treated with a combination of octreotide and bromocriptine, complete disappearance of the tumor without tumor regrowth was observed 20 months after octreotide withdrawal (25).

In the present study, the pituitary volume decreased in all but two of the subjects. In cases in which the tumor could not be demarcated from the normal pituitary tissue, this effect might have been due to tumor shrinkage as well as to reduction of the size of the normal pituitary tissue. In patients with acromegaly the normal somatotrophs are likely to be suppressed by the high levels of IGF-I, and a reduction of the normal pituitary tissue is therefore less probable. In one case, however, the normal gland seemed to decrease in size, but not the tumor. The reason for this is not clear, but it is possible that the hypointense nonenhancing area represented a portion of a cystic tumor rather than the whole tumor.

The mechanism(s) of tumor growth inhibition are not fully understood. There is no evidence for a tumoricidal effect of octreotide, as supported by the rapid regrowth of tumors after cessation of therapy (24). Morphologic heterogeneity of GH-secreting tumors has been well documented (26), as have differences in the somatostatin receptors on the adenomatous tissue (27). Microscopic examinations of pretreated GH-secreting adenomas have revealed a decrease in cell size, and in a few cases, perivascular fibrosis (20, 21). In a previous study, hypodense tumor areas were detected on CT scans obtained after therapy (20). In our study, all adenomas except one seemed to be homogeneously solid. The significance of the slightly increased signal intensity on the T2-weighted images in three cases is uncertain. In one case, an area with the appearance of a cyst

or necrosis expanded slightly during therapy. This might have been spontaneous and cannot be attributed with certainty to the treatment.

The moderate tumor shrinkage and the stability of the signal characteristics of GH-secreting adenomas during octreotide therapy contrast distinctly with the observations in prolactinomas treated with dopamine agonists, in which extensive and rapid tumor reductions, associated with necrosis and hemorrhage, are constant findings (28, 29), and necroses have been found histologically (30). This indicates that the mechanism of tumor inhibition probably differs between these two types of tumor.

In three of the present patients, we found only a minor effect on the tumor volume or no effect at all in spite of a reduction in the circulating level of GH. Two of these tumors were small, which might have made it difficult to detect small volume changes. Yet another possibility is that the three tumors may have been unusually rich in nonsomatotrophic cells, which are not responsive to the action of octreotide.

In attempts to improve the outcome of neurosurgery, the tumor-reducing effect of the drug has been explored, with varying results (9, 20, 21, 31). Pretreatment of macroadenomas with octreotide for 1 to 30 weeks, however, was associated with unusually high short-term remission rates, possibly due to the softening of the tumor tissue as observed by the surgeons (9, 20, 21). On the basis of the present observations it would appear that prolonged periods of pretreatment are needed to clarify the full potential of octreotide in improving the ultimate outcome of surgery. Reduction of the invasive components might also be beneficial before surgery.

In our opinion, MR imaging during octreotide treatment of GH-secreting adenomas is valuable, in particular during the initial phase of treatment, to ensure that the treatment is effective and to assess the maximal tumor shrinkage. There was no correlation between the tumor shrinkage and the suppression of GH secretion, in accordance with previous reports (9, 21). We therefore think that the assessment of GH levels alone is inadequate for therapy monitoring, since one of the goals of the treatment is reduction of tumor size. We suggest that after the baseline MR study, the examination should be repeated at 3 and 12 months, provided that there are no signs of tumor progression clinically or biochemically. The need of further MR examinations should thereafter be determined individually according to the therapeutic response. An additional investigation after 36 months could be valuable, since a proportion of the tumors responded with shrinkage after prolonged treatment. However, since we did not detect any tumor growth during treatment, further investigations seem unnecessary provided that GH levels remain stable. We propose the baseline MR examination be carried out with both noncontrast and contrast-enhanced T1-weighted coronal and sagittal imaging. Proton density– and T2-weighted images did not provide any additional information of clinical importance. Unenhanced T1-weighted coronal and sagittal images may be sufficient during follow-up, unless tumor reexpansion or clinical deterioration occurs, or unless surgery is anticipated. In the latter cases, contrast-enhanced images are valuable to analyze the tumor extension and the presence of hemorrhage and necrosis as closely as possible.

In summary, we have shown that octreotide causes shrinkage of GH-secreting pituitary tumors over prolonged periods of time. The stability of the MR signal characteristics indicates that necrosis and hemorrhage are not common features. Some tumors respond quickly within a few months whereas others show a more gradual response with effects observable after 4 years of treatment. In five of our patients, a mean serum GH of less than 2 μg/L and normalized circulating levels of IGF-I were obtained, indicating that in a proportion of patients long-term medical treatment is effective and can be considered as an alternative to surgery.

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