Effect of Long-term Treatment with Somatostatin Analogue (SMS 201-995) on Pituitary Tumor Shrinkage in Acromegaly

—Report of Two Cases—

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Abstract

The effect of long-term somatostatin analogue (SMS 201-995) treatment in two acromegalic patients is reported. Continuous tumor shrinkage was observed even after 129 and 139 weeks of treatment with 600 μ g of SMS 201-995 daily. A huge and firm adenoma underwent shrinkage during treatment with SMS 201-995. No serious side effect appeared during 160 weeks of treatment. SMS 201-995 has a long-term tumor shrinkage effect and improves endocrinopathies.

Key words: acromegaly, somatostatin analogue, tumor shrinkage, pituitary adenoma

Introduction

SMS 201-995, a newly developed long-acting somatostatin analogue, strongly inhibits the secretion of growth hormone (GH).²⁾ Therapeutic use is effective for patients with GH-secreting pituitary adenoma (acromegaly) refractory to surgical or bromocriptine treatment.^{3,7,11,13,16)} SMS 201-995 also causes tumor shrinkage,^{1,3,4,6-9,12-16)} previously observed in a limited number of cases treated with bromocriptine.¹⁰⁾ It therefore has an important future role in the treatment of acromegaly. However, few clinical investigations have evaluated tumor shrinkage during long-term treatment.¹⁾ We report our clinical findings, especially tumor shrinkage, in two patients with acromegaly treated for over 3 years with SMS 201-995.

Case Reports

Case 1: A 36-year-old male was admitted with progressive acral enlargement and overt diabetes mellitus on February 1, 1982. He demonstrated

typical signs of active acromegaly, such as acromegalic countenance, acral enlargement, and excessive sweating. Neurological examination found bitemporal visual field defects. Computed tomographic (CT) scans disclosed a huge invasive tumor with suprasellar, sphenoid, and cavernous sinus extension. Transsphenoidal surgery on March 8, 1982 achieved only partial tumor removal from the sphenoid sinus, because the tumor was firm and bleeding heavily. The histological diagnosis of the tumor specimen was mixed (acidophilic and chromophobic) pituitary adenoma. Postoperatively, the visual disturbance improved, but the endocrinological symptoms remained unchanged. 20 mg of bromocriptine was therefore administered daily, but was ineffective. He continued to have high blood GH levels (38–160 ng/ml). Other clinical data are shown in Table 1.

Subcutaneous SMS 201-995 injection (50 μ g every 8 hours) was begun on November 26, 1987. The dose was subsequently increased to 200 μ g every 8 hours. However, the blood GH levels rose markedly. The somatomedin-C levels also increased, despite falling

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Table 1 Endocrinological data before treatment with SMS 201-995

	Case 1		Case 2	
	Basal	Peak or nadir	Basal	Peak or nadir
Basal GH level (ng/ml) and response to:				
glucose (75 gm)	56.0	61.0	43.0	83.0
TRH (0.5 mg)	65.0	140.0	27.8	76.3
LHRH (0.1 mg)	63.0	64.0	50.0	113.1
insulin (0.1 U/kg)	not performed		26.5	86.0
bromocriptine (2.5 mg)	57.9	30.8	36.0	35.0
SMS 201-995 (50 μ g)	66.0	9.0	23.0	2.0
Plasma somatomedin-C (U/ml)	7.80		1.95	

LHRH: luteinizing hormone-releasing hormone,
TRH: thyroid hormone-releasing hormone.

Fig. 1 Case 1. Basal GH (●) and somatomedin-C levels (□) during SMS 201-995 treatment. Br: bromocriptine.

during the initial stage of treatment (Fig. 1). Different dose regimens were tried, before 50 μ g every 2 hours *via* infusion pump was finally chosen for the maintenance dosage. Details of this pro-

cedure were reported previously.¹⁵⁾ CT scans showed that the greatest tumor dimension had shrunk by 16%, from 55 to 46 mm, 29 weeks after beginning SMS 201-995 treatment (Fig. 2A, B). Magnetic resonance (MR) images showed the shrinkage to be 27%, to 40 mm, in the 129th week (Fig. 2C). SMS 201-995 treatment also improved the excessive sweating and arrested the progress of acral enlargement.

Bromocriptine was simultaneously administered from the 132nd week in an attempt to obtain a better clinical effect. The blood GH and somatomedin-C levels had stabilized at 20–30 ng/ml and 2–3 U/ml, respectively, in the 165th week (Fig. 1). No side effects due to SMS 201-995 have been observed and the insulin dosage administered for diabetes mellitus has remained unchanged.

Case 2: A 36-year-old female was admitted with progressive acral enlargement, amenorrhea, and visual disturbance on October 15, 1984. She had typical acromegalic features and right homonymous hemianopsia. CT scans showed a large tumor with suprasellar extension. Transsphenoidal surgery on October 22, 1984 achieved subtotal tumor removal, and failed to normalize blood GH levels, although the right homonymous hemianopsia disappeared completely. The histological diagnosis of the tumor specimen was acidophilic pituitary adenoma. Reoperation on September 2, 1985 also resulted in subtotal tumor removal, and failed to reduce the blood GH levels. 30 mg of bromocriptine was then administered daily, but without effect. Other clinical data are shown in Table 1.

Subcutaneous SMS 201-995 injection (50 μ g every 8 hours) was begun on January 30, 1988. The dose was subsequently increased to 200 μ g every 8 hours. The blood GH and somatomedin-C levels fell to within the normal ranges (Fig. 3), and the clinical symptoms improved. CT scans before treatment re-

Fig. 2 Case 1. Postcontrast coronal CT scans (A, B) and MR image (C) before and during SMS 201-995 treatment. A: before treatment, B: the 29th week, C: the 129th week.

Fig. 3 Case 2. Basal GH (●) and somatomedin-C levels (□) during SMS 201-995 treatment.

Fig. 4 Case 2. Postcontrast coronal CT scans (A–C) and MR image (D) before and during SMS 201-995 treatment. A: Before treatment. B: In the 27th week, decrease in the left pituitary volume (arrow) is observed. C: In the 96th week, further decrease in the left pituitary volume and shift of the pituitary stalk to the left (arrow) are observed. D: In the 139th week, persistent tumor-shrinking effect is observed.

vealed small tumor fragments in the left half of the sella turcica (Fig. 4A). In the 27th week, the volume of the sellar contents had decreased (Fig. 4B). A further decrease was seen in the 96th week, especially in the left half of the sella turcica (Fig. 4C). CT scans also showed a shift of the pituitary stalk to the left, an indirect sign of tumor shrinkage. MR images in the 139th week showed prolonged shrinkage of the tumor (Fig. 4D).

The satisfactory effect was maintained in the 156th

week (Fig. 3). No side effects, other than transient diarrhea, have been observed.

Discussion

Our two acromegalic patients received SMS 201-995 for more than 3 years, the longest treatment durations so far reported (Table 2). In addition, we were able to monitor the pituitary tumors radiologically. In Case 1, the greatest tumor dimension decreased by 16 and 27% after SMS 201-995 treatment for 29 and 129 weeks, respectively. This was a fibrous and firm adenoma, which was usually difficult to remove, but the tumor-shrinking effect definitely persisted for a long period after the start of SMS 201-995 treatment. In Case 2 as well, the tumor-shrinking effect persisted after the 27th week of treatment.

Barkan *et al.*¹⁾ administered 150–1000 µg of SMS 201-995 daily to 10 untreated cases of acromegaly, all with invasive adenoma, for 3–30 weeks. CT scans showed a 20–54% decrease in tumor volume in all cases. The maximum tumor-shrinking effect appeared within 8–12 weeks. Sassolas *et al.*¹²⁾ monitored 38 cases by CT scanning during SMS 201-995 treatment, finding that tumor shrinkage did not persist (except in 3 cases) after 6 months. In both our cases, the tumor shrinkage persisted after the period of maximum effect reported by these authors.

No detailed and systematic investigation of the tumor-shrinking effect of SMS 201-995 is available for large numbers of cases. Our cases presented no unusual characteristics in their clinical courses before drug treatment, endocrinological data, or histological findings. Case 1 was unusual, in that resistance to lowering of blood GH levels by SMS 201-995 was found during the early stage of treatment.¹⁵⁾ However, there is no clear relationship between this finding and the persistent tumor shrinkage.

Morphometric study suggests that tumor shrinkage with SMS 201-995 is caused by a decrease in both cytoplasmic and nuclear volumes, suggesting endogenous somatostatin influences these changes in the tumor ultrastructure.¹⁾ Therefore, evaluation of the tumor-shrinking effect of SMS 201-995 requires further investigation of endogenous somatostatin and intrinsic hypothalamic hormones, including GH-releasing hormone.

In Japan, SMS 201-995 treatment has been mainly used in acromegalic patients for whom surgical, bromocriptine, and/or radiation therapy were ineffective.¹³⁾ However, SMS 201-995 has caused tumor shrinkage in a number of cases of macroadenoma,^{1,4,6,12,15)} so preoperative administration should be

Table 2 Review of SMS 201-995 effect on pituitary tumor shrinkage

Author (Year)	No. of patients with tumor shrinkage	Dose of SMS 201-995 ($\mu\text{g/day}$)	Length of treatment (wks)	Degree of tumor shrinkage	Remarks
Lamberts <i>et al.</i> (1985) ⁹⁾	3/ 4 (75%)	100-300	8-24	slight	
Tolis <i>et al.</i> (1986) ¹⁶⁾	3/ 9 (33%)	50-200	6-20	—	
Chiodini <i>et al.</i> (1987) ³⁾	3/10 (30%)	100-300	30-47	30-45%	
Sandler <i>et al.</i> (1987) ¹¹⁾	0/ 8	300	12-60	—	
Spinas <i>et al.</i> (1987) ¹⁴⁾	1/ 5 (20%)	300	1-4	17%	preoperative administration
Barkan <i>et al.</i> (1988) ¹⁾	10/10 (100%)	150-1000	3-30	20-54%	<i>de novo</i> patients with grade III or IV tumors
Cozzi <i>et al.</i> (1988) ⁴⁾	12/21 (57%)	100-1500	3-35	15-90%	macroadenoma
Horikawa <i>et al.</i> (1988) ⁷⁾	7/ 9 (78%)	300-800	3-38	slight-44%	
Shimatsu <i>et al.</i> (1989) ¹³⁾	11/40 (28%)	100-1500	2-114	—	multicenter trial in Japan
Sassolas <i>et al.</i> (1990) ¹²⁾	11/23 (48%)	300-1500	24	6 cases: $\geq 50\%$ 5 cases: 20-50%	large tumors or tumor remnants (largest diameter: ≥ 20 mm)
Present report	2/ 2 (100%)	600	Case 1: 165 Case 2: 156	27% slight	fibrous adenoma

positively considered for untreated acromegalic patients to improve surgical results.^{1,14)} Pretreatment with bromocriptine in patients with prolactinoma causes useful tumor shrinkage.^{5,17)} Barkan *et al.*¹⁾ reported better remission rates for acromegalic patients receiving SMS 201-995 for 3-30 weeks before surgery, compared with acromegalic patients with similarly sized tumors not receiving the drug, and operated on by the same surgeon. Spinas *et al.*¹⁴⁾ reported that the tumors in five patients with untreated acromegaly receiving 300 μg of SMS 201-995 daily for 1-4 weeks were subsequently extirpated easily because of the soft tumor tissue and well-defined boundary from normal pituitary tissue. Horikawa *et al.*⁷⁾ also reported that treatment with SMS 201-995 before operation produced satisfactory surgical results.

Preoperative SMS 201-995 treatment may therefore significantly improve surgical results, especially in patients with macroadenoma. However, wider use of SMS 201-995 for endocrinological and tumor-shrinking treatment requires more detailed and systematic investigation of the drug dosage, and the relationship between treatment duration and tumor shrinkage, surgical results, and histology of the tumor. Preoperative treatment is often discouraged by the unsettled problem of treatment duration. The present work and Barkan *et al.*¹⁾ suggest

that this is at least 8-12 weeks. If CT scans or MR images show the tumor to have shrunk, endocrinological abnormalities have improved, and no immediate surgical decompression is necessary, then further treatment for around 30 weeks to observe tumor shrinkage before operation can be recommended.

Our two cases began treatment with SMS 201-995 approximately 3 years ago, and continue with the drug. No escape phenomena have been observed, and normalized blood GH and somatomedin-C levels persist in one. In addition, no side effects requiring discontinuance of treatment were experienced.

The present study shows that SMS 201-995 can cause tumor shrinkage for a period longer than that previously reported, and can maintain endocrinological improvement. The incidence of side effects is extremely low, even with long-term treatment. Further detailed investigation is necessary on the effect of SMS 201-995 as a pretreatment drug to improve surgical results, and the effective dosage for tumor shrinkage.

Acknowledgment

The present study with SMS 201-995 was started with patient consent after a full explanation of the nature

and purpose of the study.

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