The effect of somatostatin analogue on chiasmal dysfunction from pituitary macroadenomas

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The long-acting somatostatin analogue SMS 201-995 has been shown to be efficient in the treatment of somatotropic and thyrotropic adenomas. In some cases, it can suppress adenoma secretion and lead to tumor shrinkage. Pituitary macroadenomas are often associated with a vision-threatening chiasmal syndrome. In this series, SMS 201-995 was administered subcutaneously to eight patients with pituitary macroadenomas of various types responsible for severe long-lasting visual defects. An obvious improvement of both visual fields and acuity occurred in six patients, in two of these during the first 4 to 6 hours of treatment; in two patients, gonadotropic adenomas were unresponsive. Maximal improvement (normalization of visual fields in three cases) occurred within 6 to 45 days and was sustained during the 1- to 12-month follow-up period. This effect seems independent of the type of adenoma since the adenomas secreting growth hormone (GH) and thyroid-stimulating hormone and silent corticotropic-secreting adenomas responded as well as did two of the non-functioning adenomas. In one acromegalic patient visual improvement was obtained while the abnormal GH secretion remained unaltered. In all cases but one, no tumor shrinkage could be demonstrated. These data demonstrate that SMS 201-995 can rapidly improve the chiasmal syndrome due to pituitary macroadenoma, and suggest that this effect might be independent of a reduction in tumor volume.

Key Words: somatostatin analogue • optic chiasm • visual dysfunction • pituitary adenoma • chiasmal syndrome

The occurrence of visual disturbances is a major concern in patients with pituitary macroadenomas. They can be followed by rapid onset of visual defects that are not always reversible even if an emergency operation is performed. Moreover, surgery is often unsatisfactory since complete removal of macroadenomas can be very difficult and is seldom achieved. The long-acting somatostatin analogue SMS 201-995* is an effective treatment of acromegaly by suppressing abnormal secretion of growth hormone (GH), and volume shrinkage of GH-secreting adenomas has been documented in some cases. In the same way, thyroid-stimulating hormone (TSH) secretion by thyrotropic adenomas is inhibited by SMS 201-995. The effects of this treatment on the chiasmal syndrome due to pituitary macroadenomas remain to be evaluated. We have previously reported rapid improvement of visual defects in a patient with thyro-

tropic adenoma. This case prompted us to investigate the effect of SMS 201-995 on the chiasmal syndrome in eight patients with pituitary macroadenomas of various types. Dramatic visual improvement was observed in six patients.

Clinical Material and Methods

Eight consecutive patients referred to our department for pituitary macroadenomas with visual defects were included in this series. One of these cases has been reported briefly elsewhere. The main characteristics of each patient are summarized in Table 1. All had a pituitary macroadenoma with suprasellar extension (16 to 30.5 mm in vertical diameter) as assessed by computerized tomography or magnetic resonance (MR) imaging. All had visual defects of various duration (Table 2).

Ophthalmological evaluation was performed by the same investigator and consisted of examination of acuity, visual fields (using a Goldmann perimeter), and the
TABLE 1

Main characteristics of eight patients with pituitary macroadenoma treated by SMS 201-995*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Duration of Disease</th>
<th>Treatment</th>
<th>Adenoma Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36, M</td>
<td>10 yrs</td>
<td>none</td>
<td>somatotropic/ICC</td>
</tr>
<tr>
<td>2</td>
<td>27, M</td>
<td>8 mos</td>
<td>none</td>
<td>thyrotropic</td>
</tr>
<tr>
<td>3</td>
<td>60, M</td>
<td>27 yrs</td>
<td>none</td>
<td>thyrotropic</td>
</tr>
<tr>
<td>4</td>
<td>38, F</td>
<td>16 yrs</td>
<td>S, R; HC: 20 mg</td>
<td>silent corticotropic/ICC</td>
</tr>
<tr>
<td>5</td>
<td>61, M</td>
<td>20 yrs</td>
<td>S, R; none</td>
<td>nonsecreting/ICC</td>
</tr>
<tr>
<td>6</td>
<td>57, M</td>
<td>23 yrs</td>
<td>S</td>
<td>nonsecreting/ICC</td>
</tr>
<tr>
<td>7</td>
<td>38, M</td>
<td>2 yrs</td>
<td>none</td>
<td>gonadotropic/ICC</td>
</tr>
<tr>
<td>8</td>
<td>61, F</td>
<td>8 mos</td>
<td>S</td>
<td>gonadotropic/ICC</td>
</tr>
</tbody>
</table>

* The type of adenoma was assessed by increased pituitary hormone plasma levels and/or by immunocytochemistry (ICC) of the removed pituitary tumor. S = surgery; R = radiotherapy; B = bromocriptine; HC = hydrocortisone.

TABLE 2

Ophthalmological course in six patients during treatment by SMS 201-995

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Duration of Visual Defects</th>
<th>1st Improvement</th>
<th>Maximum Improvement</th>
<th>Follow-Up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 yrs</td>
<td>5th day</td>
<td>19th day</td>
<td>12 mos</td>
</tr>
<tr>
<td>2</td>
<td>7 mos</td>
<td>6th day</td>
<td>36th day</td>
<td>14 mos</td>
</tr>
<tr>
<td>3</td>
<td>3 yrs</td>
<td>3rd hr</td>
<td>45th day</td>
<td>8 mos</td>
</tr>
<tr>
<td>4</td>
<td>5 yrs</td>
<td>6th day</td>
<td>7th day</td>
<td>1 mo</td>
</tr>
<tr>
<td>5</td>
<td>1 yr</td>
<td>5th hr</td>
<td>6th day</td>
<td>7 mos</td>
</tr>
<tr>
<td>6</td>
<td>1 mo</td>
<td>2nd day</td>
<td>14th day</td>
<td>12 mos</td>
</tr>
</tbody>
</table>

optic fundus. Basal serum GH, somatomedin C, free thyroxine (T4), thyrotropin (TSH), prolactin, gonadotropin (luteinizing hormone and follicle-stimulating hormone), and β-endorphin levels were measured using commercially available radioimmunoassay kits. The glycoprotein hormone alpha subunit was kindly assayed by Dr. G. Faglia of Milan, Italy. Immunocytochemical study of the removed pituitary adenosomas was performed either by an immunoperoxidase technique or using indirect immunofluorescence.

In Cases 1 to 3, SMS 201-995 was used as first-line treatment. A short-term treatment was tried before surgery in Case 7. In the four remaining patients, previous surgery had failed to normalize visual defects. In all eight patients, the size of the adenoma, its invasive characteristics, or its recurrence after previous surgery made successful surgical intervention highly improbable. Five patients had giant adenosomas and the other three exhibited invasion of the sphenoidal sinus. Five of the eight patients had presented for treatment of tumor recurrence after previous surgery. At first, SMS 201-995 was administered at a dosage of 100 µg/day by continuous subcutaneous infusion, using a syringe pump as previously described. Dosage and mode of administration were then modified according to the visual and hormonal outcome.

Visual examination and endocrine evaluation were performed before treatment and repeatedly during the follow-up period (Table 2). In order to rule out any spontaneous variation or a "learning" effect, visual tests were repeated two to seven times in all patients before the treatment began; the results were stable. The patients' cooperativeness was assessed at each examination and was good in all cases.

Results

Effects of SMS 201-995 on Visual Status

Visual impairment was not clinically significantly modified in Cases 7 and 8; SMS 201-995 was therefore withdrawn after 2 days and 5 days, respectively. A dramatic and very rapid visual field improvement occurred in the other six patients. Visual impairment was ameliorated within hours after SMS 201-995 administration in two patients (Table 2). Visual acuity improved in all of these six patients and normalized within 2 days in Case 6 and within 4 days in Case 2. Complete recovery occurred in three patients (Fig. 1). In Case 6, surgery performed 2 years before the present admission had left a superior hemianopsia, after which the patient's visual fields had worsened. Administration of SMS 201-995 restored his visual fields to the previous postoperative state. Improvement of visual fields preceded amelioration of acuity in Cases 1 and 4. Acuity and visual fields improved simultaneously in the four remaining patients. Visual fields quickly worsened after SMS 201-995 withdrawal in Cases 2 and 4 and improved again when the drug was resumed (data not shown).

Maximum visual improvement occurred between the 6th and the 45th days of treatment (Table 2), and was sustained during the entire follow-up period (1 to 12 months). Neuroradiological evaluation failed to demonstrate any tumor shrinkage in five of the six patients. In Case 3, MR imaging showed that the cystic part of the thyrotropic adenoma had shrunk completely and its solid part was somewhat diminished.

Hormonal Effects of SMS 201-995

No hormonal effect of SMS 201-995 was noted in the two patients with gonadotropic adenoma whose visual involvement remained unchanged (Cases 7 and 8). Free T4, and TSH levels returned to normal in the two patients with thyrotropic adenoma (Cases 2 and 3), although TSH later partially escaped in Case 3. The patient with an asymptomatic corticotropic adenoma (Case 4) had elevated β-endorphin levels which were not suppressed by SMS 201-995.

In the acromegalic patient, SMS 201-995 was effective in improving the visual defects but not GH secretion. The mean diurnal plasma GH level (± standard deviation) was 27.6 ± 9.4 µg/liter before treatment and 24.2 ± 5.9 µg/liter on the 5th day. Hormonal levels in the two patients with nonfunctioning adenoma (Cases 5 and 6) remained unchanged during treatment.
SMS 201-995 and chiasmal syndrome

Side Effects
Side effects consisted of mild and transient abdominal discomfort at the beginning of treatment. One patient (Case 3) had abdominal cramping and steatorrhea, and developed asymptomatic gallstones.

Discussion
This report reveals that visual defects of patients with pituitary macroadenomas can be improved by SMS 201-995. The rationale for such a therapeutic trial was the previous demonstration that SMS 201-995 not only can suppress abnormal hormone secretion of GH- or TSH-secreting adenomas, but also may induce tumor shrinkage in some cases. Visual field defects and acuity improved in six of our eight patients, and even normalized in three of them. The visual improvement which occurred within a very short time after treatment had begun was sustained during the entire follow-up period of 1 to 12 months in all patients. Moreover, in Case 4 visual evoked responses improved during SMS

Fig. 1. Visual acuity and visual fields before (left) and during (right) SMS 201-995 treatment in six patients with pituitary macroadenoma. Visual fields were plotted using a Golmann perimeter with a 64-sq mm object at 1-candela/sq m light intensity (outer plot) and with 4- and 1-sq mm objects at 0.0315 candela/sq m light intensity (inner plots).
The mechanism by which SMS 201-995 acts on visual defects remains uncertain. Visual abnormalities in patients with pituitary macroadenoma are thought to be due to chiasmatic compression.\(^{10}\) Reduction of tumor volume might be responsible for visual improvement in our patients in the same way as in patients with macroadenomas treated with bromocriptine.\(^{2,11}\) Indeed, tumor shrinkage during long-term SMS 201-995 administration has been reported in GH-secreting adenomas.\(^{1,5,8}\) Such a mechanism is unlikely in our patients since the visual effects were very rapid. Moreover, no tumor shrinkage could be demonstrated at the time of visual improvement nor during the follow-up period in five of six patients. We cannot rule out subtle changes in tumor volume leading to chiasmatic decompression. Tumor shrinkage could occur through receptor-mediated mechanisms since somatostatin-binding sites have been shown on tumor cells in various types of pituitary adenomas.\(^{10}\) If such a mechanism was involved in our patients, one might expect that parallel changes would occur in both visual defects and hormonal secretion. However, the visual defects of the acromegalic patient improved while GH secretion did not, suggesting that SMS 201-995 can act independently on the optic chiasm and hormonal secretion.

It has been reported that visual fields and acuity improved very early after the introduction of dopamine agonist treatment in some patients with macroadenomas;\(^{2,11}\) similarly, in our patients, the rapid improvement suggests a vascular mechanism. Indeed it has been demonstrated that pituitary adenomas induce increased intrasellar pressure and modify local blood supply.\(^9\)

Whatever the mechanism, the impressive visual improvement observed in our patients deserved further study. In patients with pituitary macroadenoma and visual abnormalities, an emergency operation is usually the only therapeutic procedure considered and the results may be disappointing. Since in our patients visual improvement was demonstrable very early (a few hours to a few days) after SMS 201-995 treatment, such therapy could be valuable, at least as a short-term preoperative course, in similar patients. Moreover, the lack of side effects in our patients also supports the performance of an SMS 201-995 trial in such patients.

Acknowledgments

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References


