

## **SOM230, A New Somatostatin Analogue, Is Highly Effective in the Therapy of Growth Hormone/Prolactin-Secreting Pituitary Adenomas**

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**Abstract Purpose:** We have previously shown that transgenic mice ubiquitously overexpressing the *HMGA2* gene develop growth hormone/prolactin-secreting pituitary adenomas. This animal model has been used to evaluate the therapeutic efficacy of SOM230, a somatostatin analogue with high affinity for the somatostatin receptor subtypes 1, 2, 3, and 5, on the growth of the pituitary adenomas.

**Experimental Design:** Four groups of 3- and 9-month-old *HMGA2* transgenic mice were treated for 3 months with a continuous s.c. injection of two different dosages of SOM230 (5 or 50  $\mu\text{g}/\text{kg}/\text{h}$ ), one dose of octreotide, corresponding to that used in human therapy, and a placebo, respectively. The development of the tumor before and after therapy was monitored by magnetic resonance imaging of the pituitary region and evaluation of the serum prolactin levels.

**Results:** The highest dose of SOM230 induced a drastic regression of the tumor, whereas octreotide was not able to induce any significant tumor regression, although tumor progression was significantly slowed down. No significant differences were observed between the animals treated with the lowest dose of SOM230 and those receiving placebo.

**Conclusions:** These results clearly support the efficacy of the SOM230 treatment in human pituitary adenomas secreting prolactin based on the dramatic tumor shrinkage and fall in prolactin levels. This beneficial effect could be of crucial clinical usefulness in patients bearing tumors resistant to dopaminergic drugs.

Pituitary tumors account for ~15% of intracranial tumors. Although they are usually benign adenomas, they are associated with significant morbidity due to local compressive effects on brain structures and cranial nerves, leading to headaches and visual disturbances. Morbidity can also result from tumor-derived hormonal hypersecretion or following treatment that inadvertently damages adjacent normal pituitary hormone

secretion. About two thirds of pituitary tumors express and secrete pituitary hormones. Among these, prolactinomas are the most common lesions, representing ~50% of all the clinically diagnosed pituitary adenomas. The current strategy for treating patients with functional pituitary tumors aims to normalize excess pituitary hormone secretion, targeting neuroendocrine receptors with dopamine agonists and somatostatin analogues (1). This approach has the potential to abrogate or suppress excess of hormone secretion. In addition, as pituitary cell hormone secretion and proliferation are strictly linked, treatment with dopamine and/or somatostatin agonists can also inhibit pituitary tumor growth. Thus far, the only drugs widely used to treat pituitary tumors over the past 2 decades are somatostatin analogues, such as octreotide and lanreotide, which have high affinity for somatostatin receptor (SSTR) 2. They are effective in the tumor mass shrinkage of 20% to 50% of treated patients depending on the receptor density and subtype expression (2). Different somatostatin analogues have been found to have SSTR subtype specificity and have revealed functional interactions between somatostatin receptor subtypes. In fact, *in vitro* experiments have shown that SSTR2-selective ligands do not prevent prolactin release from prolactin-secreting pituitary tumor cells, whereas a SSTR5-selective analogue suppresses prolactin secretion by ~40%, indicating divergent roles for SSTR2- and SSTR5-mediated actions in prolactinomas (3). By this point of view, the development of molecules that

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bind with high-affinity different SSTR subtypes should have a superior therapeutic potential. SOM230 is a promising drug candidate that fulfills these criteria because it exhibits an almost universal binding to somatotropin release-inhibiting factor receptor subtypes (SSTR1, SSTR2, SSTR3, and SSTR5) and exerts potent inhibitory effects on the growth hormone/insulin-like growth factor-I axis in several *in vivo* animal models (4, 5). Preclinical studies on experimental models *in vivo* are needed to elucidate the real efficacy of a therapy based on SOM230 administration for functional pituitary adenomas secreting either growth hormone or prolactin or both of them. Since the last decade, several transgenic mouse models of pituitary adenomas have been generated by targeting expression of oncogenic transgenes to anterior pituitary cells using pituitary-specific promoters (6–8). Our group has recently developed a genetically engineered mouse model for pituitary tumorigenesis (9). These mice, overexpressing in all tissues the *HMGA2* gene, develop growth hormone/prolactin-secreting pituitary adenomas by 6 months of age, with an almost total penetrance in the female gender. This animal model represents an excellent model for evaluating new therapies for pituitary adenomas. Therefore, to evaluate the therapeutic efficacy of SOM230 on pituitary tumor development and hormone secretion, and to compare it with that of octreotide, four groups of 3- and 9-month-old *HMGA2* transgenic female mice were treated for 3 months with SOM230 (at two different doses), octreotide, and a placebo, respectively. SOM230, at the highest dose of 50  $\mu\text{g}/\text{kg}/\text{h}$ , drastically affected the tumor progression and induced a significant regression of the tumor. In contrast, the octreotide at the same dose significantly slowed down the progression of the tumor without inducing regression.

Therefore, these results indicate that administration of SOM230 may represent an elective treatment for pituitary adenomas secreting growth hormone and prolactin.

## Materials and Methods

**Mice and treatment.** Two groups of 32 *HMGA2* transgenic mice have been treated either at 9 months or at 3 months of age as follows: 8 placebo, 8 octreotide (50  $\mu\text{g}/\text{kg}/\text{h}$ ), 8 SOM230 (5  $\mu\text{g}/\text{kg}/\text{h}$ ), and 8 SOM230 (50  $\mu\text{g}/\text{kg}/\text{h}$ ). The treatment was delivered by s.c. injection, for 3 months, by using Alzet osmotic pumps model 2004. A saline solution (0.9% NaCl) was used as placebo. All the mice have been housed in the Animal facility of the Istituto dei Tumori di Napoli G. Pascale.

**Quantitative reverse transcription-PCR.** To evaluate SOM230-responsive SSTR expression in *HMGA2* transgenic mice pituitary tumors, the relative amount of *sst1*, *sst2A*, *sst2B*, *sst3*, and *sst5* was calculated in four tumors removed by the mice not treated by somatostatin analogues by quantitative reverse transcription-PCR. Quantitative PCR was done as described previously (10). Briefly, polyadenylated mRNA was isolated during Dynabeads Oligo(dT)25 (Dyna AS, Oslo, Norway) from tumor tissue samples. cDNA was synthesized using the polyadenylated mRNA, which was eluted from the beads in 40  $\mu\text{L}$   $\text{H}_2\text{O}$  for 2 min at 65°C, using Oligo(dT)12-18 Primer (Applied Biosystems, Foster City, CA). One twentieth of the cDNA library was used for quantification of the SSTR subtype mRNA levels. A quantitative reverse transcription-PCR was done by Taqman Gold nuclease assay (Perkin-Elmer Corp., Foster City, CA) and the ABI PRISM 7700 Sequence Detection System (Perkin-Elmer) for real-time amplification according to the manufacturer's instructions. The assay was done using 15  $\mu\text{L}$  Taqman Universal PCR Master Mix (Applied

Biosystems), 300 nmol/L forward primer, 300 nmol/L reverse primer, 200 nmol/L probe, and 10  $\mu\text{L}$  cDNA template in a total reaction volume of 25  $\mu\text{L}$ . The detection of hypoxanthine phosphoribosyl transferase (HPRT) mRNA served as a control and was used for normalization of somatostatin subtype mRNA levels.

The specific mouse primer sequences (Biosource, Nivelles, Belgium) that were used included the following: HPRT, 5'-TGAAGAGCTACTG-TAATGATCAGTCAAC-3' (forward) and 5'-AGCAAGCTTGCAACCT-TAACCA-3' (reverse); *sst1*, 5'-TTGACTTGGGGATCTGAAGG-3' (forward) and 5'-ATTAATAAGCGGCACCATCG-3' (reverse); *sst2A*, 5'-TGAGTGGTACGGAGGATGGG-3' (forward) and 5'-CTCCGTGGT-CTCATTACAGCC-3' (reverse); *sst2B*, 5'-CAAGGCAGACAATTCA-CAATCC-3' (forward) and 5'-GTTTCTGCCGGGAGCT-3' (reverse); *sst3*, 5'-CCTCTGCAGCAACCCTGTA-3' (forward) and 5'-CAGATGAAG-GATAGGTAACAGTGG-3' (reverse); and *sst5*, 5'-GCGCTCAGAACG-CAAGGT-3' (forward) and 5'-CAGCAGCCCACGAACACC-3' (reverse).

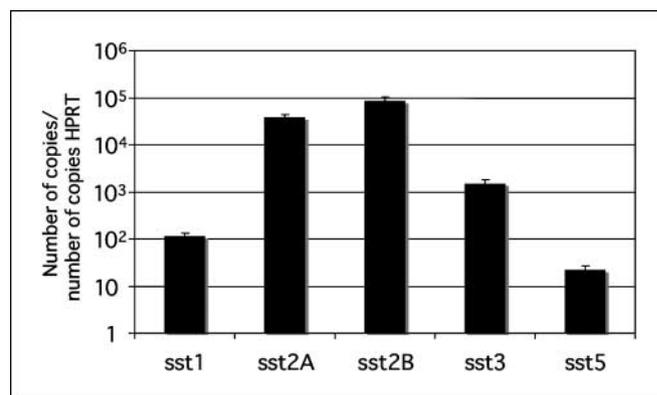
The probe sequences that were used included the following: HPRT, 5'-FAM-TGCTTTCCTGGTTAAGCAGTACAGCCC-TAMRA-3'; *sst1*, 5'-FAM-TGAAATCTCCAGGTACAGGTTTAAAGAAGTGGCA-TAMRA-3'; *sst2A*, 5'-FAM-AGAGAGCGCAGTAAAGCAGGACAAATCC-TAMRA-3'; *sst2B*, 5'-FAM-ATTGCCTGGGTGTGACCTGGTGGGA-TAMRA-3'; *sst3*, 5'-FAM-TTAGGGCTGTTGGCTGCTGACTGATCCTCATCTCAG-TAMRA-3'; and *sst5*, 5'-FAM-ACTCGCATGGTGGTGGTGGTGGTGGC-TAMRA-3'.

The relative amount of SSTR mRNA was determined by means of a standard curve generated in each experiment from known amounts of mouse genomic DNA. For the determination of the amount of HPRT mRNA, a standard curve was obtained by including dilutions of a pool cDNAs known to contain HPRT. The amount of SSTRs mRNA was calculated relative to the amount of HPRT and is given in arbitrary units.

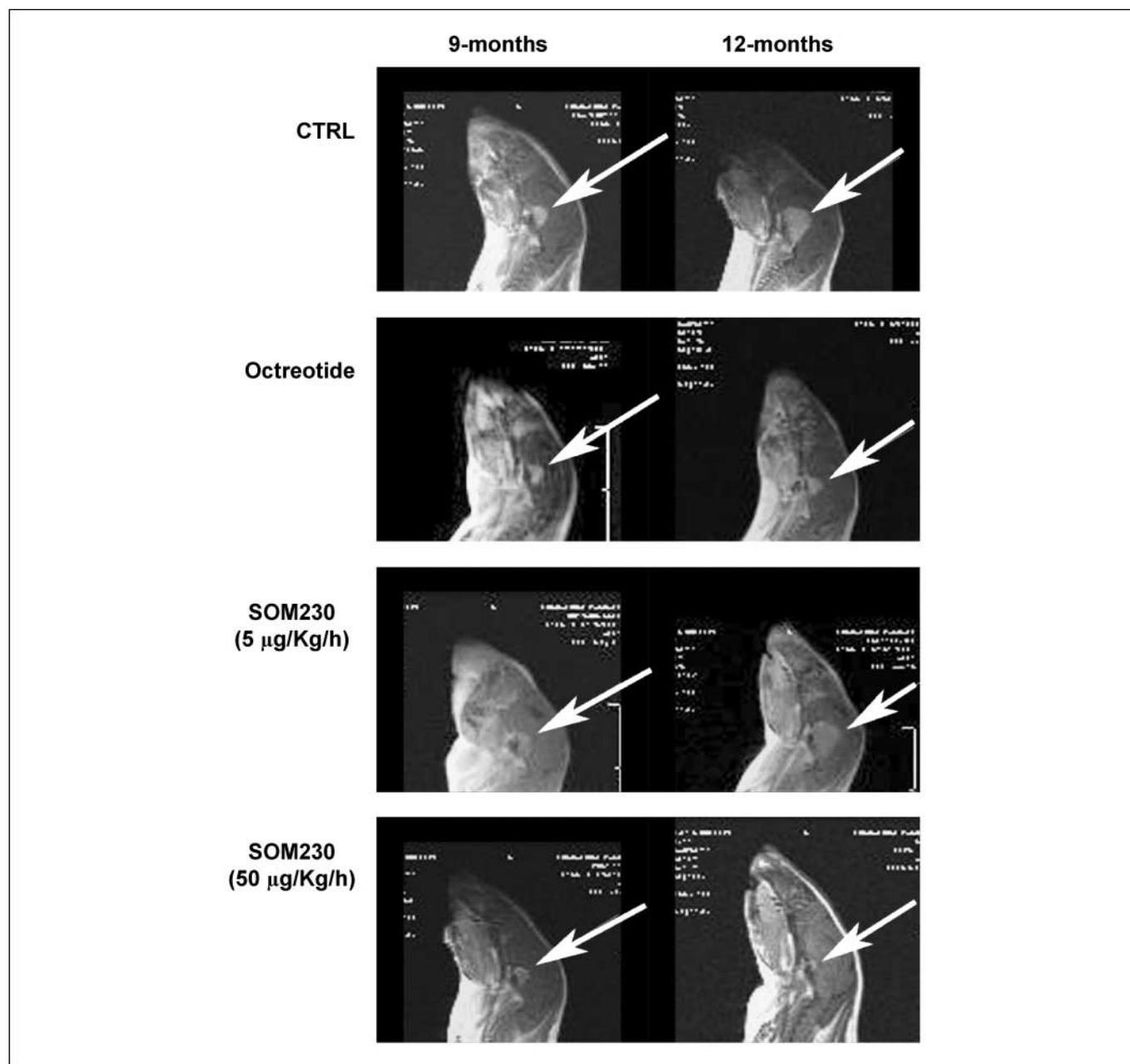
**Serum hormone measurements.** Serum prolactin concentration was measured before and after the treatment using mouse prolactin RIAs consisting of reagents provided by Dr. A.F. Parlow (National Hormone & Peptide Program, Harbor-UCLA Medical Center, Torrance, CA).

**Magnetic resonance.** Magnetic resonance imaging (MRI) analyses have been done at the Istituto dei Tumori di Napoli G. Pascale on a 1.5-T magnet system using local receiver coils and an 8-cm field of view. Sagittal slices (3 mm thick) have been obtained with T1-weighting (repetition time/echo time = 400/11 ms). The images were analyzed by Acrobat Photoshop; the tumor size, expressed in pixel, has been obtained by the product of the two major diameters of the lesion as appeared in the median sagittal section.

**Histologic analysis.** Histologic evaluation was done on 10% neutral phosphate-buffered formaldehyde-fixed, paraffin-embedded pituitary adenomas. Paraffin sections were stained with H&E and Gordon-Sweet silver impregnation to assess reticulin fiber network, which is essential



**Fig. 1.** SSTR expression in pituitary adenomas from *HMGA2* transgenic mice. The results obtained from three independent real-time analyses of *sst1*, *sst2A*, *sst2B*, *sst3*, and *sst5* genes were plotted as a histogram, showing their relative copy number compared with the housekeeping *HPRT* gene.



**Fig. 2.** MRI of HMGA2 transgenic mice before and after the treatment at 9 to 12 months of age. Representative mouse for each treated group before (*left*) and after (*right*) the treatment. Arrows, pituitary adenoma.

for distinguishing normal adenohipophysial architecture, hyperplasia, and adenoma.

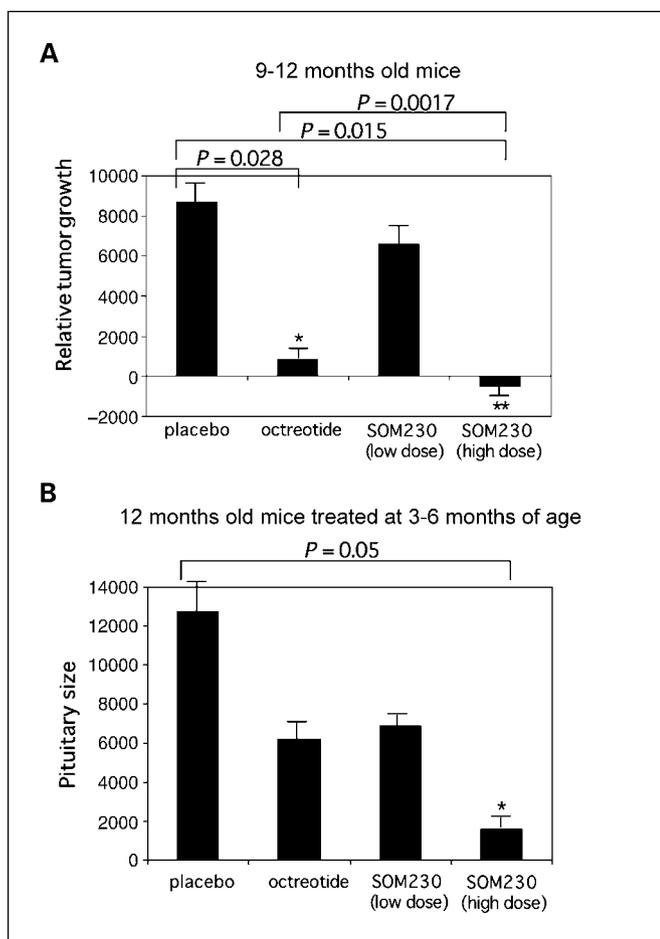
**Statistical analysis.** For the comparison of statistical significance between two groups, Student's *t* test was used. A *P* value of <0.05 was considered statistically significant.

## Results

**Characterization of SSTRs in pituitary tumors from HMGA2 transgenic mice.** A significant relative amount of *sst1*, *sst2A*, *sst2B*, *sst3*, and *sst5* was found in the pituitary tumors removed by HMGA2 mice. The number of *sst2A* and *sst2B* is significantly higher than that of all the others, although a rather heterogeneous expression of the formers and a rather homogeneous

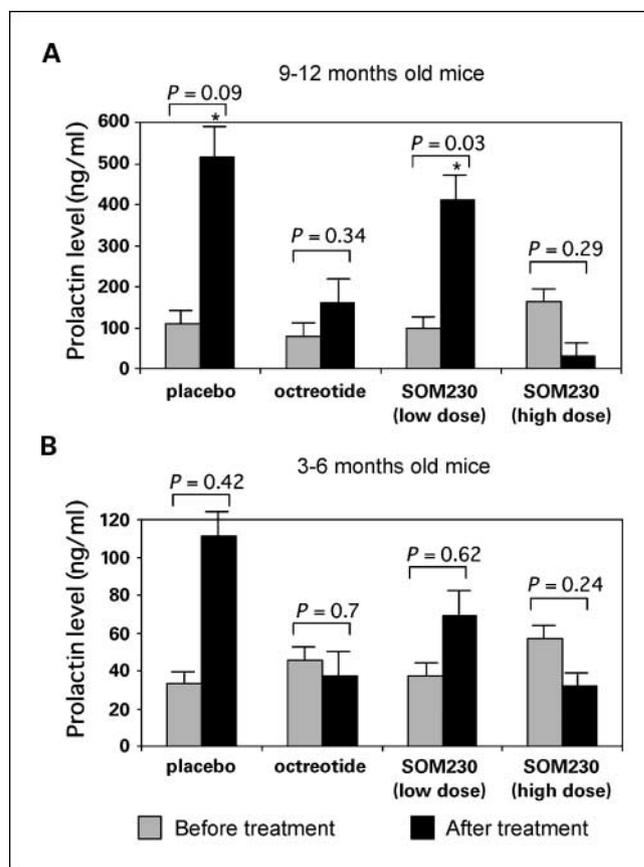
expression of the latter were found. The expression of SSTRs is shown in Fig. 1.

**Treatment of HMGA2 transgenic mice with SOM230 reduces tumor proliferation.** The expression of SSTR subtypes 1, 2, 3, and 5 by the pituitary adenomas occurring in the HMGA2 transgenic mice might account for testing the SOM230 for their treatment. Female HMGA2 transgenic mice were used for preclinical studies with SOM230 because they develop growth hormone/prolactin-secreting pituitary adenomas with an almost complete penetrance. SOM230 was given to 3- and 9-month-old mice by continuous s.c. injection as indicated in Materials and Methods. In parallel, we also used octreotide and a placebo as positive and negative control of pituitary adenoma treatment, respectively.



**Fig. 3.** Size analysis of tumors in treated mice. *A*, mice treated at 9 mo of age were analyzed by MRI before treatment and 3 mo later at the end of the treatment. Tumor size was evaluated as indicated in Materials and Methods. Columns, mean of the size difference before and after the treatment for each animal group; bars, SE. *B*, mice treated at 3 mo of age were analyzed by MRI only at 12 mo of age and 6 mo later at the end of the treatment when the tumor was easily detectable. Tumor size was evaluated as before. Columns, mean tumor size for each treated group; bars, SE. Top of the graphs, *P* value obtained by the comparison of the groups. Asterisks, values that differ statistically from the placebo group.

In 9-month-old mice, tumor growth was monitored before and after the treatment by MRI analysis (Fig. 2). The comparison of the images clearly shows a decrease of tumor size in mice treated with high dosage of SOM230 (50  $\mu\text{g}/\text{kg}/\text{h}$ ). Conversely, a clear increase in tumor size was observed in mice treated with either a placebo (control) or a low dosage of SOM230 (5  $\mu\text{g}/\text{kg}/\text{h}$ ). Finally, no increase in tumor size was shown in mice treated with octreotide. We measured tumor size for each mouse before and after the treatment as indicated in Materials and Methods and plotted the results as shown in Fig. 3A. The comparison of groups revealed that the pituitary tumors of HMGA2 transgenic mice significantly ( $P = 0.028$ ) slow down their growth in response to 50  $\mu\text{g}/\text{kg}/\text{h}$  octreotide. Interestingly, 50  $\mu\text{g}/\text{kg}/\text{h}$  SOM230 significantly ( $P = 0.015$ ) affect the tumor progression of HMGA2 transgenic mice, even better than octreotide does, resulting in a reduction of the tumor size. In fact, the effect of SOM230 on tumor proliferation is significantly stronger ( $P = 0.0017$ ) than that exerted by the octreotide.



**Fig. 4.** Serum prolactin concentration measurement in treated mice. *A*, columns, mean prolactin levels before and after the treatment at 9 mo of age for each animal group; bars, SE. *B*, columns, mean prolactin levels before and after the treatment at 3 mo of age for each animal group; bars, SE. Top of the graphs, *P* value obtained by the comparison of the value in each group. Asterisks, values obtained after the treatment of each group, whose difference from the value of the same group before the treatment is statistically different.

In 3-month-old mice, tumor growth was monitored by MRI (data not shown) only at 12 months of age (after 6 months from the end of the treatment) to follow up the tumor growth in mice that received the treatment before the onset of the tumor. As shown in Fig. 3B, tumor size, as appeared by MRI analysis at 12 months of age, was measured for each treated mouse. The only group that showed a significant size reduction compared with placebo-treated mice ( $P = 0.053$ ) was that treated with SOM230 at high dosage (50  $\mu\text{g}/\text{kg}/\text{h}$ ). Conversely, both octreotide and 5  $\mu\text{g}/\text{kg}/\text{h}$  SOM230 did not significantly reduce the tumor size compared with a placebo ( $P = 0.23$  and  $0.35$ , respectively). Importantly, no side effects were observed

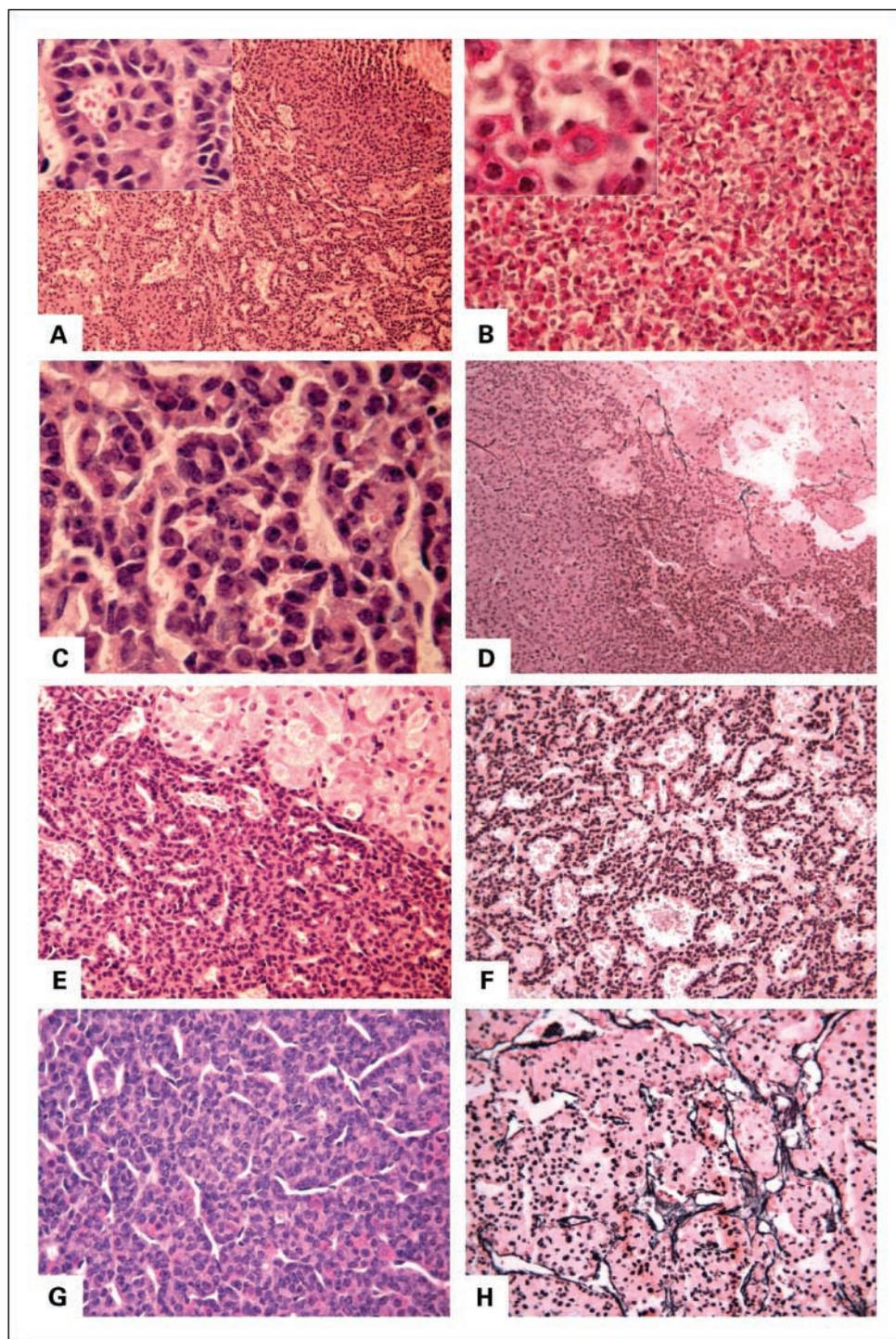
**Table 1.** Incidence of pituitary adenomas in treated mice

Treatment	Age at the time of treatment	
	3 mo, n (%)	9 mo, n (%)
Placebo	8/8 (100)	8/8 (100)
Octreotide	8/8 (100)	8/8 (100)
SOM230 (low dose)	6/8 (75)	8/8 (100)
SOM230 (high dose)	2/8 (25)	2/8 (25)

in treated mice over the period they were infused and no differences in terms of body weights were observed among the animals at the end of the treatment.

**HMGA2 transgenic mice treated with SOM230 show reduced prolactin secretion.** Plasma prolactin concentration in transgenic mice before and after the treatment was measured by RIA. In mice treated at 9 to 12 months of age, prolactin levels were significantly increased in both placebo-treated and SOM230-treated (low dose) mice in comparison with the respective control mice (placebo group:  $P = 0.09$ ; SOM230 (low dose):

$P = 0.03$ ). Conversely, octreotide-treated mice did not increase significantly their prolactin levels ( $P = 0.34$ ) and SOM230-treated (high dose) mice showed a trend to decrease prolactin concentration following treatment, although it was not statistically relevant ( $P = 0.29$ ; Fig. 4A). In mice at 3 to 6 months, the prolactin levels were not significantly increased even in the placebo-treated mice because of the still low tumor growth due to the early stage at this age. Nevertheless, a trend versus a slower increase or a mild decrease was observed in all the other treated groups in comparison with the respective controls (Fig. 4B).



**Fig. 5.** Cytohistologic characterization of the pituitary tumors in treated mice. *A*, transgenic mice of the placebo group developed sharp delineated pituitary tumors with a follicular type architecture and several blood lakes. *B*, a healthy pituitary gland from a wild-type mouse is shown for comparison. *C*, mice treated with octreotide show the same phenotype as in (*A*). *D*, in most neoplastic cells from octreotide-treated mice, the reticulin network was lost. *E*, mice treated with SOM230 (low dose) show the same phenotype as in (*A*) and (*C*). *F*, in most neoplastic cells from SOM230-treated (low dose) mice, the reticulin network was lost. *G*, total rescue of the normal phenotype was observed in mice treated with SOM230 (high dose). *H*, intact reticulin network in pituitary cells from SOM230-treated (high dose) mice. *A*, *B*, *C*, *E*, and *G*, H&E staining. *D*, *F*, and *H*, Gordon-Sweet silver stain. Original magnifications,  $\times 100$  [*A* and *B* (main images) and *D-H*] and  $\times 400$  [*A* and *B* (insets) and *C*].

**Decreased incidence of pituitary tumors in mice treated with SOM230.** All the pituitary glands and tumors from treated mice were fixed in formalin and analyzed by H&E staining for the characterization of the histologic phenotype and the obtaining of the definitive diagnosis. The results of this analysis are summarized in Table 1.

In Fig. 5, some representative histologic analyses are shown. Most of mice treated with 50  $\mu\text{g}/\text{kg}/\text{h}$  SOM230, both at 3 and 9 months of age, reacted to the therapy with a complete rescue of the normal phenotype (Fig. 5G). The same result was achieved by only one fourth of the mice treated with 5  $\mu\text{g}/\text{kg}/\text{h}$  SOM230 at 3 months of age. All the other treated mice showed a clear tumoral phenotype with histologic characteristics similar to the placebo group (compare Fig. 5C and E with Fig. 5A), although mice treated with either octreotide, both at 3 and 9 month of age, or SOM230 (low dose), at 3 months of age, showed in most cases smaller tumors compared with control transgenic mice (data not shown). The Gordon-Sweet silver method was used for the histologic diagnosis of these nodules and showed focal disruption of the reticulin fiber network, which is pathognomic for the adenomatous transformation of pituitary cells (Fig. 5D and F).

## Discussion

Our previous studies proposed a crucial role of the *HMGA2* gene overexpression in pituitary tumorigenesis. In fact, *HMGA2* was found amplified and overexpressed in human prolactinomas, and transgenic mice overexpressing the *HMGA2* gene developed pituitary adenomas secreting growth hormone and prolactin. Therefore, this animal model may represent a unique tool for testing the efficacy of new drugs for the therapy of human pituitary adenomas. Currently available treatment for human pituitary adenomas uses somatotropin release-inhibiting factor analogues, such as octreotide and lanreotide, which bind preferentially and with high affinity to sst2 (11). Therefore, a research of new drugs able to compete with the other receptors has been prosecuted. Recently, a new drug molecule, SOM230, which binds with high affinity to all human somatotropin release-inhibiting factor receptor subtypes, except for sst4, has been identified and characterized (5). It has the potential to act as a drug combination that contains both sst2- and sst5-selective somatotropin release-inhibiting factor analogue agonists and that was shown to inhibit growth hormone release more potently than single-agent treatment in pituitary adenoma cultures (3, 12). Moreover, the affinity of SOM230 to sst5 suggests potential inhibitory effects on prolactin secretion, given that it has been found that sst5-selective agents inhibit prolactin secretion from prolactinomas, whereas sst2-selective agonists were inactive (12).

A recent study by the group of Melmed compared the relative efficacy of SOM230 and octreotide on hormone secretion from

primary cultures of rat pituitaries, human fetal pituitary tissues, and pituitary adenomas, finding no significant improvement by SOM230 on growth hormone and prolactin suppression compared with octreotide, although a trend toward greater efficacy of SOM230 in both growth hormone-secreting and prolactin-secreting adenomas, compared with octreotide, was suggested (13). In the current study, the relative efficacy of octreotide and SOM230 on hormone secretion and tumor growth was studied in our *in vivo* model of pituitary tumorigenesis, such as the *HMGA2* transgenic mice, by a 3-month continuous s.c. infusion of the different compounds. Our results clearly show that the treatment with SOM230 at the dose of 50  $\mu\text{g}/\text{kg}/\text{h}$  is extremely effective because it is able to induce a drastic regression of the tumor when the treatment was started while the tumor was already evident. When the treatment was begun at the third month after birth, no pituitary tumor being present, it gave rise to the prevention of the neoplastic phenotype. Conversely, the treatment with octreotide did not lead to the regression of the disease and could not avoid the development of the tumor in mice treated for 3 months before the onset of the tumor. However, the compound showed a certain efficacy because the growth of the tumor was less rapid in the octreotide-treated compared with mock-treated animals. Interestingly, no effect at all was achieved after the treatment with SOM230 at the dosage of 5  $\mu\text{g}/\text{kg}/\text{h}$ , suggesting that the treatment with SOM230 requires a minimal dosage to get a valid effect.

The results of this study indicate the potential usefulness of SOM230 in the treatment of human prolactinomas. It is widely accepted that dopaminergic compounds, such as bromocriptine and cabergoline, are extremely effective in normalizing prolactin levels and reducing tumor mass, up to its disappearance, in 80% to 90% of patients in different series (14–17). The minority of patients with tumors resistant to dopaminergic drugs are very difficult to treat and have potentially the risk of further tumor progression with neurologic damage and even death because of the tumor (18). The results of the current study support the possible usefulness of SOM230 in patients with prolactinomas, especially in those patients who are resistant to cabergoline.

In conclusion, these results taken together propose the treatment with SOM230 as a valid tool for the therapy of human pituitary adenomas with an efficacy that it is higher in comparison with that obtained with octreotide, currently used for the treatment of human prolactinomas. However, our data also show that the dosage of SOM230 must be appropriate because a low dosage does not give any therapeutic effect.

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