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Somatostatin Analogs in Treatment of Non-Growth Hormone–Secreting Pituitary Adenomas

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Besides well-known effects in GH-secreting adenomas, somatostatin analogs such as octreotide and lanreotide have been used in TSH-secreting adenomas and in the so-called clinically nonfunctioning adenomas. The rationale for their use is based on the evidence that both these tumor types express large amounts of somatostatin receptor subtypes 2 and 5, which are preferentially bound by octreotide and lanreotide. However, whether in TSH-secreting adenomas the results are excellent in the nonfunctioning type, the results are controversial. Some preliminary results showing a very rapid recovery of the visual field have not been confirmed subsequently. No evident effect of tumor shrinkage has been reported. At present, the use of somatostatin analogs in clinically nonfunctioning adenomas is questioned.

Key Words: Pituitary adenomas; somatostatin; octreotide; lanreotide.

Introduction

Somatostatin is a peptide consisting of 14 amino acids, so called because of its ability to inhibit growth hormone (GH) release, originally detected accidentally while searching the distribution of GH-releasing factor in the hypothalamus of rats *(1)*. However, subsequently other investigations considerably expanded its initial role of a GH-inhibiting factor, and it is now well known that somatostatin plays an inhibitory role in the regulation of several organ systems in humans and other species, such as the central nervous system, hypothalamus and pituitary gland, gastrointestinal (GI) tract, endocrine and exocrine pancreas, several components of the immune system, retina, and cardiovascular system *(2,3)*. Besides inhibiting GH and thyroid-stimulating hormone (TSH) secretion, somatostatin inhibits a variety of other secretions and functions such as insulin, glucagon, secretin, vasoactive intestinal polypeptide, pancreatic enzymes, bile and colonic fluid such as secretion as well as GI motility, and gastric acid production *(2,3)*.

However, the need for iv administration, its short half-life in the circulation, and the postinfusion rebound hormone hypersecretion prevented the clinical use of somatostatin. To overcome these limitations, synthetic somatostatin analogs have been synthesized, and two of them, octreotide and lanreotide, are available for treatment in humans. It should be considered, however, that native somatostatin has high affinity for all five somatostatin receptor (SSTR) subtypes, designated SSTR1–5 and belonging to the seven-transmembrane domain receptor family, while octreotide and lanreotide have high affinity only for the SSTR2 and SSTR5 and mild affinity for the SSTR3. The inability of the two available analogs to bind with high affinity all receptor subtypes explains the evidence that in a proportion of patients they fail to normalize hormone hypersecretion. This finding has been clearly demonstrated in patients with acromegaly, the largest series of patients treated so far with this class of compounds *(4–9)*. Nevertheless, both octreotide and lanreotide have been used, successfully or not, in other pituitary adenoma histotypes (i.e., glycoprotein hormone–secreting adenomas and the so-called clinically nonfunctioning adenomas).

This review focuses on the effect of somatostatin analogs in non-GH-secreting adenomas, reporting current data of clinical treatments mainly in TSH-secreting and clinically nonfunctioning adenoma since no data are available in prolactin (PRL)-secreting and adrenocorticotropic hormone–secreting adenomas.

TSH-Secreting Pituitary Adenomas

TSH-secreting adenomas are rare, frequently are macroadenomas at diagnosis, and thus present with mass effect symptoms such as headache, visual disturbance, together with variable symptoms and signs of hyperthyroidism *(10,11)*. Transsphenoidal surgery is considered the first treatment approach to these tumors; it led to normalization of thyroid hormone levels and the disappearance of pituitary tumors in 44% of patients and normalized thyroid hormone secre-

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tion despite incomplete tumor removal in 25% of cases *(10)*. However, since most of these macroadenomas tend to be locally invasive, surgery alone fails to normalize TSH and thyroid hormone levels in more than 50% of cases *(10–12)*. As routine adjunctive therapy in adults who have undergone unsuccessful surgery, radiotherapy is recommended *(10)*. Pharmacotherapy is also considered as a second line of treatment. Dopamine agonists have been shown to display scant effects in TSH-secreting adenomas *(13)*.

By contrast, because adenomas express a high amount of SSTRs *(14,15)*, somatostatin analogs have been utilized to complete the effects of surgery with high success. TSH levels have been reported to normalize in approx 80% of patients and tumor shrinkage to occur in 50% of cases during treatment with sc octreotide *(10,11,16–18)*. Octreotide treatment was also considered useful preoperatively because it allows an easier tumor removal *(10)*. The dose of octreotide in patients with TSH-secreting adenomas to achieve TSH normalization was reported to be lower than that needed to suppress GH in GH-secreting adenomas *(10)*. Similarly, lanreotide at a dose of 0.5 mg was demonstrated to inhibit acutely TSH secretion in TSH-secreting adenomas in the same amount of 0.15 mg of octreotide *(19)*. Lanreotide treatment was similarly shown to suppress plasma TSH levels and to normalize serum-free levorotatory thyroxine (fT_4) and serum-free triiodothyronine (fT_3) levels, suggesting its use in the long-term medical management of these adenomas *(20)*. In the latter open multicenter study including 18 patients with TSH-secreting adenomas, lanreotide was given at a dosage of 30 mg every 14 or 10 d for 6 mo. Plasma TSH levels decreased significantly with a parallel significant decrease of α-subunit, fT_3, and fT_4 levels (Fig. 1). No significant change in adenoma size was found in this series *(20)*. Side effects were mild and transient, none of the patients developed gallstones, and none were withdrawn from treatment for side effects *(20)*.

A recent multicenter study reported treatment with the slow-release formulation of octreotide (octreotide LAR) in TSH-secreting adenomas *(21)*. Eleven patients received sc octreotide (at dosages of 200–900 μg/daily) first and then octreotide LAR (at 20 mg, every 28 d) after a 4-wk washout period (Fig. 2). Both formulation significantly reduced TSH, fT_3, and fT_4 levels without causing significant side effects *(21)*. Interestingly, there was no difference in the TSH-lowering effect of sc octreotide or octreotide LAR (Fig. 3).

In our personal experience, in five cases with TSH-secreting pituitary adenomas, TSH levels were successfully normalized (Fig. 4), with either the analog or the formulation that we used, and thyroid hormones were normalized and remained normal throughout the treatment period. The dosage of sc octreotide, lanreotide, or octreotide LAR required to normalize TSH, fT_3, and fT_4 was indeed low (300 mg/d, 30 mg every 14 d, and 10 mg every 28 d, respectively) compared with dosages generally required in patients with GH-secreting adenomas; however, the few cases treated do not allow any firm conclusion, and dosage should be titrated on the basis on individual patients' responsiveness and tolerance, as for patients bearing acromegaly.

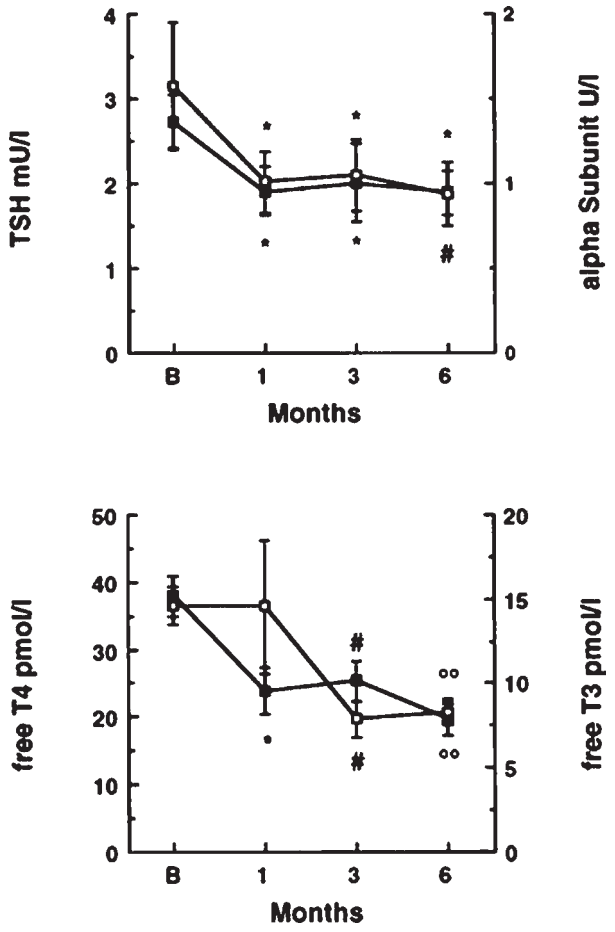

Fig. 1. Mean (± SEM) plasma TSH (■) and fAS (□) levels (**top**) and fT_4 (■) and fT_3 (□) levels (**bottom**) measured just before next injection of somatostatin analog. B, basal levels. $*p < 0.05$; $\#p < 0.003$; ○ $p < 0.0005$. (From Kuhn, J. M., Arlot, S., Lefebvre, H., et al. (2000). *J. Clin. Endocrinol. Metab.* **85,** 1487–1491. Permission granted by the Endocrine Society.)

In conclusion, either lanreotide or octreotide, sc and LAR, successfully suppresses TSH levels, inducing normalization of thyroid hormone levels in the large majority of patients with TSH-secreting adenomas. At present, long-term data using somatostatin analogs are still limited and the effects of tumor shrinkage very scant. However, because of the high success rate and the notable effect on clinical symptoms and heart rate, pharmacotherapy with octreotide and lanreotide can be applied as first therapy in patients to be submitted to surgical tumor excision in order to facilitate anesthesiology procedures.

Luteinizing Hormone, FSH-Secreting, and Clinically Nonfunctioning Pituitary Adenomas

FSH- and luteinizing hormone (LH)–secreting tumors that present with clinical symptoms of hormone hypersecre-

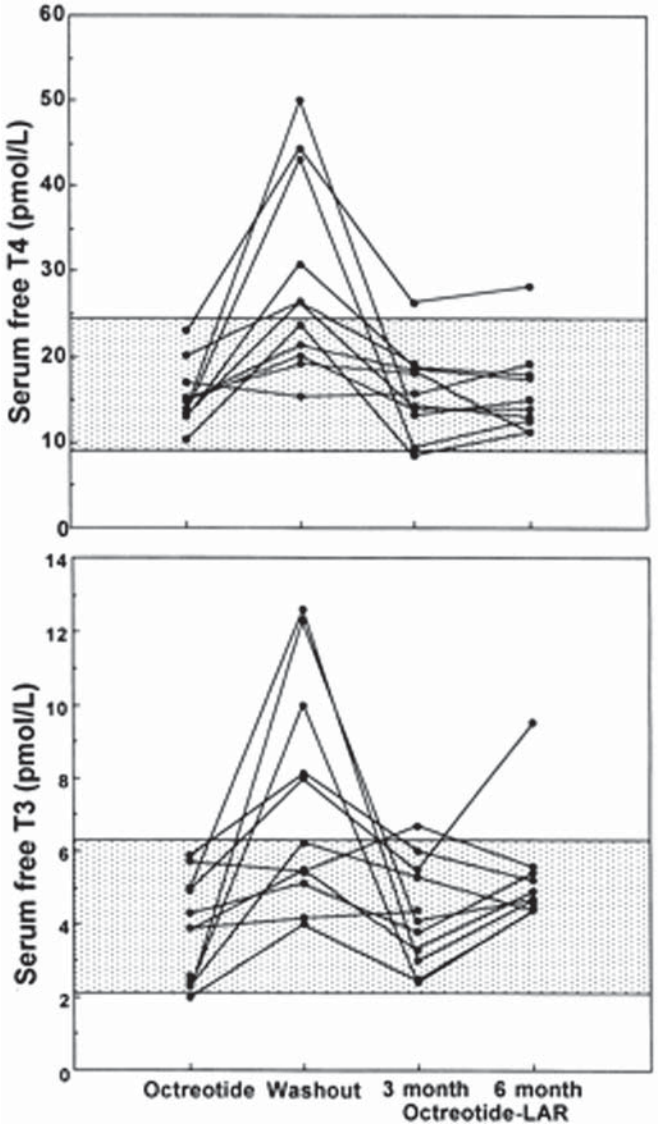

Fig. 2. Changes in serum-free T_4 and T_3 concentrations in 11 patients with TSH-secreting pituitary adenoma during octreotide- and octreotide LAR treatments. The shaded area indicates the normal range of free thyroid hormone concentrations. (Caron, P., Arlot, S., Bauters, C., et al. (2001). *J. Clin. Endocrinol. Metab.* **86,** 2849–2853. Permission granted by the Endocrine Society.)

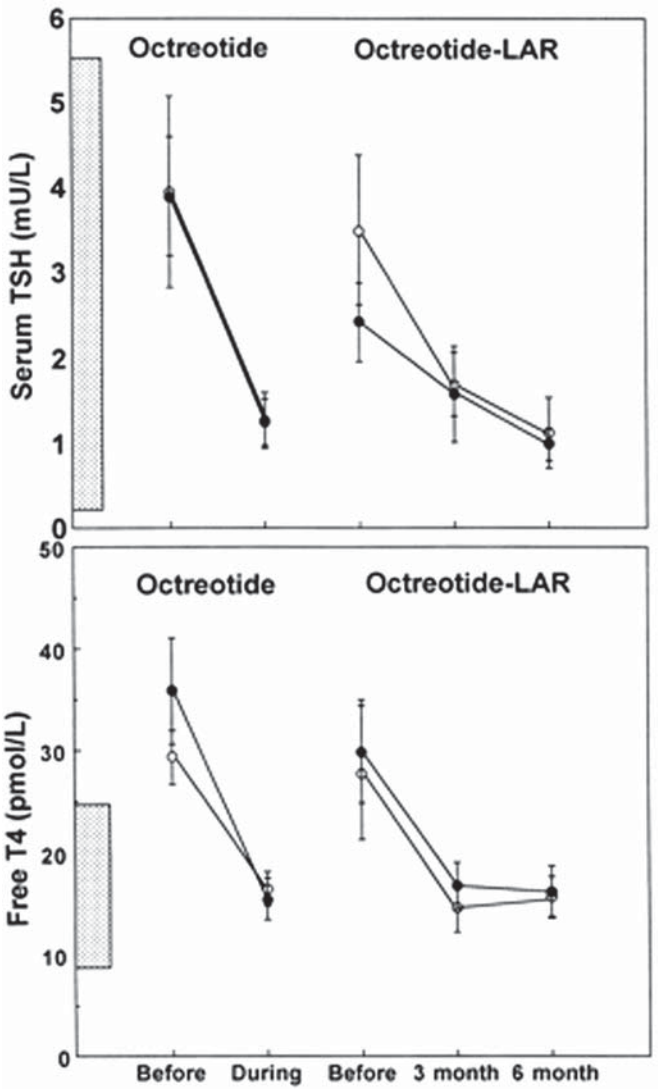

Fig. 3. Mean TSH and free T_4 (mean ± SEM) before and during sc octreotide or im octreotide LAR treatment in seven patients who underwent surgical resection and/or pituitary radiation (group 1; ●) and in four untreated patients (group 2; ○) with TSH-secreting pituitary adenoma. The shaded area indicates the normal range of TSH and free T_4 concentrations. (Caron, P., Arlot, S., Bauters, C., et al. (2001). *J. Clin. Endocrinol. Metab.* **86,** 2849–2853. Permission granted by the Endocrine Society.)

tion are very rare *(12)*. Clinically nonfunctioning pituitary adenomas (NFAs) represent a very heterogeneous group of tumors because a consistent proportion of them (up to 90%) are shown to secrete low amounts of intact FSH and LH and/or their α- and β-subunits either in vitro or in vivo *(22)*. As for TSH-secreting adenomas, the first approach to NFA is transsphenoidal surgery to remove tumor mass and decompress parasellar structures. Surgery has a low morbidity and leads to improved visual loss in the majority of cases, and hypopituitarism is partially recovered in some patients *(23–25)*. Postoperative radiotherapy is administered to patients with subtotal tumor removal, to prevent tumor regrowth and even reduce residual tumors, but it is burdened by a high prevalence of panhypopituitarism *(25–27)*.

Medical therapy has its rationale after surgery to delay radiotherapy and the potential occurrence of hypopituitarism and has its experimental basis on the high expression of dopamine and SSTRs on tumor cells *(28–32)*. This review does not discuss the results of dopamine agonist treatment, but it should be considered that patients with a high density of dopamine using in vivo scintigraphy by ^{123}I-methoxybenzamide experienced several degrees of tumor shrinkage

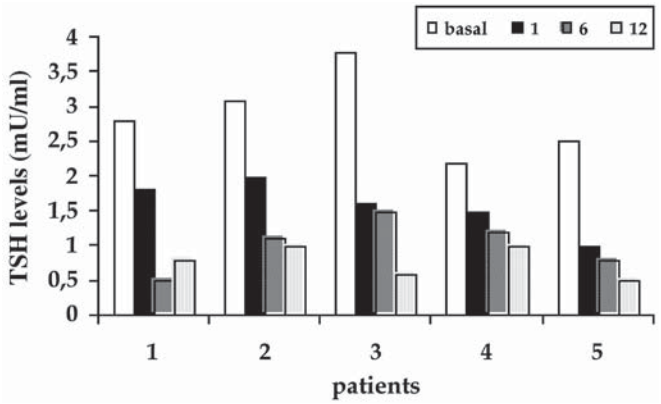

Fig. 4. Serum TSH levels before and after 1, 6, and 12 mo of therapy with somatostatin analogs. Patients nos. 1–3 received sc octreotide at doses of 300, 200, and 300 mg/d, respectively; patient no.4 received 30 mg of lanreotide every 20 d and patient no. 5 received 10 mg of octreotide LAR every 28 d (unpublished data).

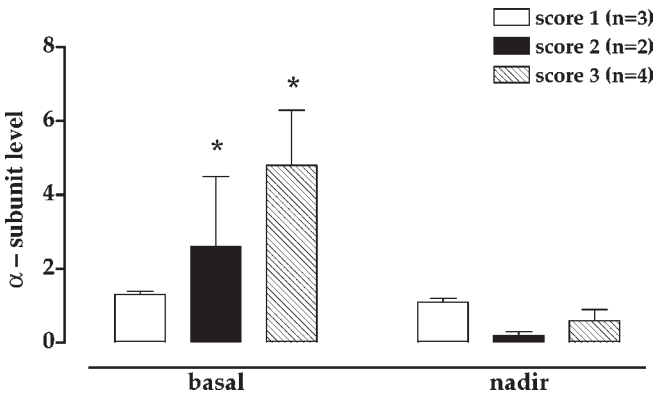

Fig. 5. Serum α-subunit levels in patients with clinically nonfunctioning adenomas before and after treatment with sc octreotide. Data are shown as mean ± SEM and separately according to uptake to ^{111}In-DTPA-D-Phe^{1}-octreotide. (From ref. *35*.)

(28,29). Whether this approach might be useful in patients with NFA, in whom the lack of biochemical markers makes monitoring of the efficacy of pharmacotherapy very difficult, is still unknown, and large, controlled studies are required.

The evidence that NFAs express SSTRs allowed reseachers to attempt treatment with somatostatin analogs *(28,31–33)*. Besides favorable antiproliferative effects of octreotide treatment on NFA cells in vitro *(34)*, a few clinical trials have been reported in NFA, but tumor reduction was observed only in 11–13% of cases, indicating a weak correlation between SSTR expression and treatment efficacy with octreotide in these patients *(31–33,35,36)*. Furthermore, Duet et al. *(33)* demonstrated that even in all five cases with NFA that had pituitary uptake of ^{111}In-pentatreotide, only the patient with very high uptake (index of 15.1) had dramatic tumor shrinkage after octreotide treatment. Similarly, we reported *(35)* significant tumor shrinkage (≥30% of baseline size) in two of six NFA during long-term octreotide therapy. We also found a significant correlation between percentage of α-subunit suppression after 6–12 mo of octreotide therapy and tumor-to-background ratio in both early ($r = 0.738$; $p = 0.003$) and late images ($r = 0.8$; $p = 0.01$). In fact, as shown in Fig.5, α-subunit levels were significantly reduced in the six patients with moderate to intense uptake of ^{111}In-DTPA-D-phe^{1}-octreotide calculated on the pituitary background ratios *(35)*.

A still unexplained finding was reported by Warnet et al. *(36)* and confirmed by De Bruin et al. *(37)*: octreotide treatment was followed by a rapid improvement in headache and visual disturbances, without any change in tumor volume. This effect was likely not owing to a direct effect on tumor size but more likely to a direct effect on the retina and the optic nerve *(38)*. A still poorly investigated pharmacologic management in NFA is based on a combined treatment of somatostatin analogs and dopamine agonists. This approach is based on data in acromegaly in which combined treatment with octreotide or lanreotide plus bromocriptine, quinagolide, or cabergoline induces a more evident suppression of GH and insulin-like growth factor-1 levels than each single drug given alone *(39–42)*. The recent experimental demonstration that SSTR5 and dopamine receptor subtype 2 can heterodimerize *(43)* gave further support to the clinical data in acromegaly. Recently, 6 mo of combination therapy with sc octreotide and cabergoline at dosages of 200 μg thrice daily and 0.5 mg/d was reported to induce >10% tumor shrinkage in 6 of 10 patients with NFA *(44)*. Following these results, we attempted a combined treatment of lanreotide (60 mg every 14 d) plus cabergoline (0.5 mg every alternate day) for 6 mo in a small series of 10 patients with NFA undergoing pharmacotherapy after unsuccessful surgery (preliminary data). Patients were selected on the basis of confirmed histologic diagnosis of NFA, a ≥10-mm maximal residual tumor diameter at magnetic resonance imaging 3 mo after surgery, and no immediate need of radiotherapy. We investigated the effect on tumor residual mass and on visual signs. After 6 mo the residual volume was decreased from 9.8 ± 2.1 to 6.7 ± 2.1 cm^3 ($p = 0.04$) and mean defect at visual perimetry improved from −14.5 ± 0.6 to −9.5 ± 1.2 at right eye ($p = 0.0006$) and from −11.9 ± 2.4 to −7.7 ± 1.8 at left eye ($p = 0.02$).

In conclusion, somatostatin analogs in patients with NFA have not been proven to have any efficacy besides the well-known expression of somatostatin analogs on the tumor membrane of these adenomas. The possibility that a combined therapy with somatostatin analogs and dopamine agonists in NFA should still be proven, even if preliminary data seem to suggest a potential application of the combined scheme in selected patients unsuccessfully operated on while waiting for radiotherapy.

Conclusion

The efficacy of somatostatin analogs in non-GH-secreting pituitary adenomas should still be proven in NFA, although it is well demonstrated in TSH-secreting ones. In these latter adenomas, the occurrence of severe cardiac consequences, mainly those at the cardiac rhythm, indicates that somatostatin analogs can be employed preoperatively. With the currently available analogs (i.e., octreotide and lanreotide) that bind with high affinity only SSTR2 and SSTR5, it is not possible to treat other pituitary tumor histotypes, even if experimental results show a high PRL-suppressive effect of agonists selective for the SSTR5 *(45,46)*. The development of new analogs with selectivity for different SSTR subtypes *(47)* or with affinity for more SSTR subtypes, such as a recent new compound named SOM230 *(48)* will open new perspectives in the pharmacologic approach to pituitary and nonpituitary neuroendocrine tumors by somatostatin analogs.

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