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Treatment of Pituitary Tumors

Somatostatin

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Somatostatin is an important physiological regulator of neuroendocrine function across multiple biological systems, including the brain and the gastrointestinal tract. In the pituitary gland, somatostatin regulates the secretion of hormones such as growth hormone and thyroid-stimulating hormone in healthy and pathological states. The short half-life of somatostatin makes it unsuitable for clinical use in chronic diseases, which led to the development of long-acting somatostatin analogs for the treatment of acromegaly and thyroid-stimulating hormone–secreting adenomas, which were administered by intermittent injection twice or three times a day. More recently, depot versions have been developed that permit dosing once every month. This review assesses the efficacy of somatostatin analogs in the treatment of pituitary adenomas, including acromegaly, thyroid-stimulating hormone–secreting tumors, non-functioning adenomas, and Cushing's disease.

Key Words: Somatostatin analogs; pituitary; acromegaly; TSH-secreting adenoma; non-functioning adenoma; Cushing's disease.

Introduction

Pituitary tumors comprise approx 10–15% of intracranial tumors at surgery and 6–23% of intracranial tumors at autopsy *(1)*. They can develop from all adenohypophyseal cell types and may be clinically active or inactive, based on their secretion of intact hormones. Local invasion, significant mass effects, and a heavy burden of clinical symptoms can occur in a large proportion of patients with pituitary adenomas *(2)*. Pituitary tumors are overwhelmingly adenomatous in nature; pituitary carcinomas are rare, with less than 100 cases being reported to date in the literature *(3)*. Patients with a pituitary tumor can present with a combination of local symptoms that are directly attributable to mass effects on surrounding structures (headache, visual disturbances) and systemic symptoms due to hormonal disturbance.

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Treatment options for patients with pituitary tumors include neurosurgery—usually via the transsphenoidal route—radiotherapy, and medical therapies. In all pituitary tumor types except for prolactinomas, surgery by a dedicated pituitary neurosurgeon is the initial treatment of choice, if the patient is willing or suitable to undergo the intervention. Radiotherapy can be particularly useful in patients with tumors that are resistant to surgery or that are rapidly expanding. In the case of clinically active tumors, however, the onset of hormonal control post-radiotherapy can be slow and medical therapy may be necessary in the interim period.

Somatostatin plays a physiological role in the regulation of various pituitary hormones, particularly growth hormone (GH) and thyroid-stimulating hormone (TSH). Owing to its short circulating half-life of 1-2 min, native somatostatin does not represent a viable therapy for chronic conditions caused by pituitary tumors, such as acromegaly due to a GH-secreting tumor. Long-acting somatostatin analogs, such as octreotide, were developed approx 20 yr ago and have been used for the treatment of pituitary tumors, particularly acromegaly *(4)*. Once-monthly depot formulations of these long-acting somatostatin analogs have been used extensively in the past decade and have improved hormonal control and patient compliance. This review assesses the use of somatostatin analogs in the treatment of pituitary tumors, including acromegaly, TSH-secreting adenomas, Cushing's disease, and clinically non-functioning adenomas.

Somatostatin and Somatostatin Receptors

Somatostatin was first described in 1973 by Brazeau et al. *(5)* as a hypothalamic polypeptide that inhibits the secretion of pituitary GH. Subsequently, somatostatin has been shown to be expressed throughout the central and the peripheral nervous system and in a wide range of other tissues, such as the gastrointestinal tract, the pancreas, the thyroid, adrenals, the placenta, the kidney, the retina, and the immune system *(4,6)*. Two biologically active forms of somatostatin are synthesized, somatostatin-14 and somatostatin-28. They are generated by proteolytic cleavage of a 92-amino-acid precursor, pro-somatostatin, which is, in turn, derived from the 116-amino-acid prepro-somatostatin. Although the relative amounts of the two isoforms vary in different tissues, somatostatin-14 and somatostatin-28 have overlapping physiological functions *(7)*. Somatostatin generally inhibits

hormonal secretion throughout multiple organs: in the pituitary, it suppresses secretion of GH, prolactin, TSH, and ACTH, while in the gastrointestinal tract and pancreas, somatostatin inhibits cholecystokinin, gastric inhibitory polypeptide, gastrin, motilin, neurotensin, secretin, glucagon, insulin, and pancreatic polypeptide *(4,6)*. Acting indirectly via these hormones and also via separate direct effects, somatostatin inhibits exocrine secretion of amylase in salivary glands and hydrochloric acid and pepsinogen in gastrointestinal mucosa, suppresses pancreatic enzyme and bicarbonate release from pancreatic acini, and inhibits biliary flow *(7)*. Somatostatin also reduces gastrointestinal and biliary motility, alters intestinal absorption of nutrients and ions, and decreases vascular smooth muscle tone *(8)*. Acting as a neurotransmitter, somatostatin has both stimulatory and inhibitory activities in the brain *(9,10)*. Moreover, somatostatin has shown immunomodulatory properties, such as reducing the production of immunoglobulins A, M, and E by B-lymphocytes and altering interleukin-2, -4, -10, and interferon-γ secretion by T-lymphocytes *(7)*. Additionally, somatostatin exerts an antiproliferative effect on normal and tumor cells *(11–13)*. The actions of somatostatin-14 and -28 are mediated by a family of five G protein–coupled somatostatin receptors sstr1–5, of which sstr2 exists in two splice variants, sstr2A and 2B. *(14–16)*. Sstr2 and 5 are the main receptors found in the adenohypophysis *(17,18)*. The prevailing receptor subtype in pituitary somatotrophs is sstr2, which is also present in many corticotrophs and gonadotrophs *(17–19)* In acromegaly, sstr2 mRNA was found in the majority of GH-secreting tumors and in a significant number of non-functioning adenomas, while there was no expression of sstr2 in prolactinomas and corticotropinomas *(20)*. Sstr5 is present in most GH-secreting tumors and prolactinomas. High levels of sstr3 mRNA can be detected in most tumors irrespective of classification, while sstr4 is undetectable *(20,21)*.

All five sstr are coupled to inhibition the adenyl cyclase activity via a pertussis toxin–sensitive protein ($G\alpha_{1-3}$) and decrease intracellular Ca^{2+}, suggesting these effects might be involved in the antisecretory action of somatostatin *(9)*. Moreover, somatostatin activate phosphotyrosine phosphatase and MAP kinases, which may contribute to somatostatin-induced antiproliferative effects *(9)*. In addition, it has been shown that somatostatin induces apoptosis selectively through sstr3 in a p53-dependent manner and through sstr2 in a SHP-1–dependent manner in normal and tumor cells *(22–24)*. Each sstr subtype is likely to exert distinct biological effects, on account of their tissue-specific expression and particular signaling mechanisms *(25)*.

Somatostatin Analogs

Native somatostatin-14 has a plasma half-life of less than 3 min and is a relatively unselective inhibitor of GH and pancreatic hormones, such as insulin and glucagon, which limits its clinical utility. Beginning in the early 1980s, various series of long-acting somatostatin analogs were developed to overcome these pharmacological limitations. The first of these to be clinically useful, octreotide, has a half-life of approx 90 min and inhibits GH, glucagon, and insulin 45, 11, and 1.3 times more potently than native somatostatin *(26,27)*. Octreotide binds with a high affinity to sstr2 and sstr5 (sstr2>sstr5), with moderate affinity to sstr3, and low affinity for sstr1 and sstr4 *(4)*. Other analogs such as lanreotide and vapreotide have a broadly similar pharmacological profile to octreotide, with high-affinity sstr2 binding.

Somatostatin analogs were initially available as intermittent subcutaneous injectable formulations, which were administered two or three times daily. Experience with the beneficial effects of octreotide administered by a subcutaneous infusion pump led to the development of a depot formulation of the drug with the aim of maximizing patient compliance/acceptance and improving hormonal control. Octreotide long-acting repeatable (LAR) consists of octreotide-impregnated biodegradable DL-lactide-co-glycolide microspheres. After deep intramuscular injection, octreotide is released from the microspheres and concentrations initially peak within 1 h; thereafter, octreotide levels plateau after the first week post-administration *(28–30)*. Octreotide concentrations fall gradually after d 42; thus, octreotide LAR is ideally administered once monthly, although less frequent dosing can be effective *(31)*. The peak-to-trough variations in dose following depot administration of octreotide (and other somatostatin analogs) is approx 25% compared with nearly 10 times this amount during intermittent subcutaneous therapy. A slow release formulation of lanreotide, lanreotide SR, has also been used widely. The formulation of lanreotide SR is ideally given approximately every 14 d *(32–34)*. More recently, an aqueous microparticle form of lanreotide, lanreotide Autogel, has been developed in Europe and shown to be effective and well tolerated in the treatment of acromegaly *(35–37)*.

Radiolabeled somatostatin analogs, such as [^{111}In-DTPA] octreotide, have been developed as diagnostic agents, relying on relatively selective sstr2 binding to identify neuroendocrine tumors expressing this receptor subtype *(38)*. Other analogs that contain radioemitting moieties like [DTPA, Tyr^3] octreotide, have been harnessed as potential somatostatin receptor–directed radiotherapy *(14)*.

Somatostatin Analog Treatment of Acromegaly

Acromegaly is caused by chronic hypersecretion of GH, which leads to a subsequent increase in insulin-like growth factor-I (IGF-I) levels *(39)*. In the overwhelming majority of cases, GH hypersecretion is due to a somatotroph adenoma of the anterior pituitary; the remaining cases are caused

by hypothalamic or ectopic secretion of GH or GH-releasing hormone. Acromegaly is characterized by overgrowth of the extremities, soft tissue swelling, and progressive disfigurement. These physical changes are accompanied by important pathological processes, such as cardiac dysfunction, hypertension, arthropathy, cancer, insulin resistance, and diabetes mellitus *(39)*. In cases where surgery is feasible, transsphenoidal resection of a pituitary adenoma is the preferable primary therapy for acromegaly. A sizeable proportion of patients—particularly those with macroadenomas—fail to achieve adequate biochemical control following surgery and require adjuvant therapy *(39)*. In patients for whom surgery is either unfeasible or unsuccessful, somatostatin analogs are the mainstay of treatment. Indeed, in patients that are undergoing surgery, somatostatin analog therapy is often implemented preoperatively in order to improve the physical status of the patient and achieve a variable degree of tumor shrinkage (see below) or alteration in tumor consistency *(40)*.

The concept of primary medical therapy with somatostatin analogs has become prevalent in the past decade *(41)*. The genesis of this approach lies in the concept that patients with a low chance of surgical cure (i.e., complete resection) of their pituitary adenoma could benefit equally from medical treatment alone. Original data supporting this concept came from a multicenter trial in the United States and Canada that identified a group of patients who did not undergo surgery and had a similar reduction in GH and IGF-I compared to patients receiving adjuvant post-operative octreotide therapy *(42)*. Patients receiving primary somatostatin analog therapy can indeed experience biochemical control; however, this is not invariably the case. Petrossians et al. reported hormonal control rates with somatostatin analog therapy in a series of 24 acromegalic patients before and after gross total resection or debulking of a pituitary adenoma *(43)*. Preoperative somatostatin therapy controlled IGF-I in 45.8% of patients, whereas in post-operative somatostatin analog treatment, the IGF-I was normalized in 78.3%. Based on these data it appears that patients with large, surgically unresectable tumors can benefit from debulking/partial tumor resection, which increases the likelihood of subsequent biochemical control with a somatostatin analog.

Hormonal Control

Early studies using the intermittent subcutaneous injected form of octreotide demonstrated significant reductions in both GH and IGF-I during short- and long-term therapy *(44,45)*; these results were confirmed in later multicenter trials *(46,47)*. In a North American multicenter study of 115 patients with acromegaly, Ezzat et al. showed that 6 mo treatment with octreotide "controlled" GH and IGF-I in 53% and 66% of patients, respectively *(48)*. The cutoff for GH control in the study was 5 μg/L, a level that has subsequently been revised downward in current guidelines *(49)*. These biochemical results were maintained in during long-term follow up *(50)*. A series of similar studies have been performed using long-acting depot formulations of somatostatin analogs for the treatment of acromegaly. The efficacy profiles of these depot formulations are broadly similar to their intermittent subcutaneous counterparts *(51)*, but have the advantages of greater ease of use and patient compliance.

Systematic reviews examining the efficacy of depot and intermittently administered somatostatin analogs in acromegaly have been performed recently *(51–54)*. In the first of these by Freda in 2002, the criteria used for GH control was a mean/nadir GH <2.0–2.5 μg/L or a post-OGTT GH concentration of <1.0 μg/L *(51)*. IGF-I control was defined as normalization for the appropriate age range. Patients were divided into two groups: those receiving adjunctive somatostatin analog therapy after other treatments and those receiving primary medical therapy. In 301 patients undergoing adjunctive octreotide LAR therapy, GH control was achieved in 56% of cases, while GH levels were controlled in 49% of 404 patients treated with lanreotide SR. IGF-I was normalized in 66% and 48% of patients treated with octreotide LAR and lanreotide SR, respectively. In patients receiving primary somatostatin analog therapy (irrespective of formulation), GH control was achieved in 50% of patients (range 27–77%), while IGF-I normalization occurred in 60% of cases (range 28–90%). These data were updated recently in a meta-analysis that included studies published up to 2003 *(53)*. The criteria for inclusion in this meta-analysis were duration of treatment of ≥3 mo, five or more subjects studied, clear and specific GH/IGF-I data reporting with information on the numbers of patients achieving control according to these criteria. Overall, the study found that biochemical control of GH and IGF-I secretion was achieved in a greater proportion of patients treated with octreotide LAR than with lanreotide SR. Responsiveness to somatostatin analogs before the study was a predictor of the likelihood of IGF-I—but not GH—control. Compared with patients receiving primary octreotide LAR, those receiving adjuvant octreotide has a greater likelihood of IGF-I control.

Control of Signs and Symptoms

In acromegalic patients receiving somatostatin analogs, symptomatic improvements can occur quite rapidly, well before objective changes in soft tissue swelling are seen. All somatostatin analog formulations exhibit similar efficacy in terms of symptom control, with up to 75% of patients noting improvements *(46,48,51)*. One symptom of acromegaly that is particularly sensitive to somatostatin analog therapy is headache. In some cases headache due to acromegaly has been reported to diminish in intensity within hours, leading to the suspicion that this may be due to an analgesic effect mediated directly or indirectly via somatostatin receptors *(55–61)*. Somatostatin analog therapy can improve acro-

megalic cardiomyopathy both functionally by increasing left ventricular ejection fraction, exercise workload, and exercise duration and also histopathologically by improving cardiac myocyte structural appearance *(62,63,64)*. Significant decreases in left ventricular mass, interventricular septal thickness, and left ventricular posterior wall thickness has also been demonstrated in acromegalic patients treated with octreotide LAR for 6 mo *(65)*. Acromegalic cardiomyopathy appears reversible with long-term somatostatin analog treatment in young patients with short disease duration; long-standing pathological changes in the heart are less amenable to improvement following biochemical control *(66)*. Similarly, bone and joint pathologies, which are frequent in acromegaly, may not reverse following hormonal control despite some improvements in associated rheumatological symptoms *(39)*. In hormonally controlled acromegaly, ongoing rheumatological complaints represent one of the major negative impacts on patients' quality of life scores *(67,68)*.

Tumor Shrinkage

Somatostatin analogs are associated with a variable degree of pituitary tumor shrinkage in up to half of patients *(69)*. The mechanisms underlying this shrinkage are incompletely understood, and a wide variety of morphological changes are noted in resected tumor tissue following somatostatin analog therapy *(70)*. Combinations of fibrosis and alterations in cell and granular content/morphology have been reported in GH-secreting pituitary adenomas after octreotide therapy. Apoptosis or other evidence of cytotoxicity have not been demonstrated, indicating that tumor size reduction induced by somatostatin analogs is probably due to adenoma cell shrinkage *(71,72)*.

Bevan recently reported a systematic review of the effects of somatostatin analogs on tumor size in acromegaly *(54)*. Following intermittent subcutaneous octreotide therapy of variable duration (data were derived from 22 studies), 45% of patients had some degree of tumor shrinkage. In patients receiving octreotide LAR the overall tumor shrinkage response rate was 57%. In a pooled analysis of approx 900 patients treated with any somatostatin analogs formulation, tumor shrinkage was seen to occur in 42% of the cases. When primary and adjunctive somatostatin analog therapies were considered separately, tumor shrinkage was seen in 52% and 21% of patients, respectively *(54)*. In a more limited dataset of 15 studies, Melmed et al. recently reported that significant tumor shrinkage with somatostatin analog therapy was defined as 10% to >45% by the various investigators *(52)*. In these studies, significant tumor shrinkage occurred in 34–37.8% of patients. The mean magnitude of tumor shrinkage seen across the dataset was 19.4% overall, and 13.4% in patients receiving long-acting depot formulations. Somatostatin analog-induced tumor shrinkage may be temporary, as re-expansion has been reported following treatment withdrawal *(28,48,73–75)*. Recent systematic reviews have put the rate of continued growth of tumors on somatostatin analog therapy at 1.4–2.7% of cases *(53,54)*.

Somatostatin Analog Treatment of TSH-Secreting Pituitary Tumors

Pituitary tumors that secrete TSH comprise 1% of all functioning pituitary adenomas and are an infrequent cause of hyperthyroidism *(76)*. Patients with TSH-secreting adenomas present with signs and symptoms of hyperthyroidism that are frequently associated with mass effects of the tumor. In adenomas that co-secrete TSH and prolactin or GH, a mixed picture of acromegaly and/or amenorrhea–galactorrhea can occur *(76)*. Unlike other causes of hyperthyroidism (e.g., autoimmune), TSH-secreting adenomas occur equally in both sexes *(77)*.

The recognized biochemical abnormalities seen in patients with TSH-secreting pituitary adenomas include elevated levels of free T_4 and free T_3 in the presence of a measurable TSH, a high free glycoprotein α-subunit (α-SU) level and/or a high α-SU/TSH molar ratio, an abnormal TSH response to a T_3 suppression test and a blunted TSH response to a TRH test *(76)*. TSH-secreting pituitary adenomas are usually macroadenomas with varying grades of invasiveness; only 15% of TSH-secreting adenomas are microadenomas *(76)*. While transsphenoidal surgery is the preferred primary treatment, the physiological inhibitory effect of somatostatin on TSH secretion *(78)* and the presence of somatostatin receptors on TSH-secreting adenomas *(79)* have made somatostatin analogs a viable medical therapy for these patients. Octreotide treatment suppresses TSH and α-SU secretion in more than 90% of cases of TSH-secreting tumors and normalizes TSH/α-SU concentration in 75% of cases *(76)*. Thyroid hormone levels are normalized by octreotide in 70–96% of (non-thyroidectomized) patients during long-term studies *(76)*. As in acromegaly, somatostatin therapy is associated with some degree of adenoma shrinkage in about 50% of patients with TSH-secreting tumors *(77,80,81)*, while visual improvements have been reported in up to three quarters of patients *(76)*. Given the rarity of TSH-secreting pituitary adenomas, relatively limited long-term data on treatment outcomes with somatostatin analogs are available *(79,80,82)*. One of the largest case collection concerns 43 patients with TSH-secreting adenomas from six centers in Belgium and France *(83)*. A total of 26 patients received somatostatin analogs as first-line treatment for a mean duration of 6 mo, and 19 of these patients subsequently underwent pituitary surgery. A significant reduction in TSH secretion and a euthyroid state were achieved in 18 of these 19 patients after 2 wk of somatostatin analog therapy, while tumor shrinkage was seen in 3/11 cases treated for at least 3 mo. Preoperative somatostatin analog therapy did not, however, influence the success of subsequent surgery. Seven patients received somatostatin analogs as sole therapy for a mean duration of 24 mo,

and thyroid hormone levels were normalized in all cases. No tumor shrinkage was seen during sole somatostatin analog therapy in evaluated patients.

Somatostatin Analog Treatment of Non-Functioning Pituitary Tumors

Non-functioning pituitary adenomas are by definition incapable of producing intact or functional hormones and, therefore, do not present with a typical hormone excess–related syndrome. Presentation may occur due to tumor mass effects, which can include visual disturbances, headaches, or other pituitary hormone defects due to extension/invasion by a non-functioning macroadenoma. Transsphenoidal surgery remains the optimal choice for primary therapy, and adjuvant radiotherapy may be useful to reduce the risk of adenoma recurrence or slow re-growth of an incompletely resected tumor *(84)*. The role of somatostatin analogs (or other medical therapies) in the management of non-functioning pituitary adenomas is limited. Some non-functioning pituitary tumors express somatostatin receptors, which can be functional, as somatostatin administration can suppress α-SU release from primary nonfunctioning pituitary tumor cell cultures *(85)*. Somatostatin and lanreotide can inhibit the proliferation of non-functioning adenoma cells in vitro *(86)*. Despite these positive data, clinical trials with somatostatin analogs in non-functioning adenomas have been relatively disappointing. In a multicenter French study, somatostatin receptor positivity was demonstrated by octreotide scintigraphy in 62% of 29 patients with non-functioning pituitary adenomas *(87)*. The negative predictive value for visual improvement of octreotide scintigraphy was 100%, although the positive predictive value was only 61%, limiting its clinical utility. In a series of 24 patients with non-functioning adenomas treated with octreotide, visual improvement was noted in 13/24 patients after 4 d, in 10/23 patients at 1 mo, and in 9/22 patients after 2 mo *(88)*. At the end of 2 mo therapy, tumor shrinkage had occurred in three cases and one tumor had increased in size (despite an improvement in visual fields). From these and other data it appears that somatostatin analog therapy may have a minor role to play in the management of non-functioning pituitary adenomas, particularly in terms of improving visual field deficits *(89)*.

Somatostatin Analog Treatment of ACTH-Secreting Pituitary Tumors

ACTH-secreting pituitary adenomas causing Cushing's disease usually present with typical endocrine manifestations rather than with tumor mass effects as they are 16 predominantly microadenomas. As such, transsphenoidal surgery is the treatment of choice for ACTH-secreting adenomas, while radiotherapy may be used in patients with refractory disease despite surgery. Medical therapy of ACTH-secreting tumors relies mainly on drugs that inhibit adrenal corticosteroid production (e.g., ketoconazole). Somatostatin analogs have been shown to be of little benefit in the clinical management of ACTH-secreting pituitary tumors, despite the observation that octreotide can inhibit ACTH release in Cushing's disease due to ectopic ACTH secretion, and can reduce acute ACTH release from corticotropinoma cells in vitro *(90–94)*. There is preliminary evidence that the new "universal" somatostatin analog, SOM230, which binds with relatively high affinity to all somatostatin subtypes (versus the relative sstr2 selectivity of octreotide/lanreotide), may be more promising for use in ACTH-secreting pituitary tumors *(95,96)*.

Conclusion

Somatostatin analogs have been available for clinical use in various formulations for about 20 yr, and in this time they have been used extensively in the clinical management of pituitary tumors. In the treatment of acromegaly and TSH-secreting pituitary adenomas, somatostatin analogs are now a mainstay of therapy, both as primary treatment and for adjunctive use after pituitary neurosurgery. More recent depot versions of octreotide and lanreotide optimize the balance between clinical efficacy and patient acceptance. Somatostatin analogs have a minor role to play in the medical treatment of ACTH-secreting and non-functioning pituitary tumors, which rely predominantly on surgical management. The most frequent pituitary tumor type, prolactinoma, is more ideally managed with dopamine agonists, which are generally effective in terms of tumor size and symptom control, and are administered orally. New research with somatostatin analogs has led to the development of "universal" ligands, such as SOM230, which bind multiple somatostatin receptor subtypes with high affinity and may have improved efficacy in ACTH-secreting pituitary tumors and other tumors that express subtypes apart from somatostatin receptor subtype 2.

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