ANNIVERSARY REVIEW

Octreotide, 40 years later

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Abstract

Octreotide remains 40 years after its development a drug, which is commonly used in the treatment of acromegaly and GEP-NETs. Very little innovation that competes with this drug occurred over this period. This review discusses several aspects of 40 years of clinical use of octreotide, including the application of radiolabeled forms of the peptide.

*European Journal of
Endocrinology*
(2019) **181**, R173–R183

Introduction

A peptide inhibiting the release of growth hormone (GH) was accidentally detected in the hypothalamus of rats during studies of the distribution of GH-releasing factor (1). This peptide, called somatostatin, is a peptide hormone that plays an inhibitory role in the regulation of multiple physiological functions, including pituitary, pancreatic and gastrointestinal hormone secretion (2, 3). Somatostatin exerts its biological effects by interaction with specific somatostatin receptors (SSTs) expressed on target tissues. Five human receptor subtypes have been detected (SST 1–5), each mediating a distinct signaling pathway (4, 5). In clinical applications, only SST2 and SST5 play an important role so far (6).

Somatostatin acts in different organ systems as a neurohormone, a neurotransmitter or as local factor acting via autocrine or paracrine mechanisms. In his Nobel lecture, Guillemin summarized a number of potential problems with regard to the clinical application of somatostatin (7): in view of its ability to inhibit such a variety of physiological processes, he predicted that somatostatin might be of therapeutic value in clinical conditions involving hyperfunction of the organ systems mentioned above. However, the multiple simultaneous effects of pharmacological concentrations of somatostatin in different organs, the need for intravenous administration, its short half-life in the circulation, and the post-infusion hypersecretion of hormones considerably hampered the

initial enthusiasm for its clinical use. From 1978 on, a number of drug companies started programs to synthesize long-acting somatostatin analogs.

Octreotide (SMS 201-995) was one of the first biologically stable somatostatin analogs to be synthesized (8): it has a much longer half-life in the human circulation than somatostatin and binds with a high affinity to SST2 (9). The structure of natural somatostatin and octreotide is shown in Fig. 1. In patients with acromegaly subcutaneously administered octreotide suppressed GH secretion without a rebound hypersecretion (10). A long-acting repeatable formulation (Octreotide-LAR) was introduced for intramuscular administration later.

Lanreotide, another metabolically stable somatostatin analog with a similar high SST2 binding profile (11), was introduced shortly after octreotide. Lanreotide is now available in a subcutaneously administered sustained-release formulation (Lanreotide-Autogel). Octreotide and lanreotide have very similar characteristics both with regard to tolerability and efficacy (vide infra).

Adverse effects

Common adverse effects of octreotide treatment include nausea, abdominal cramps, diarrhea, flatulence and fat malabsorption (12). These symptoms start within hours

Figure 1

The structure of natural somatostatin-14 and octreotide.

after injection of the drug, their severity is dose dependent, and they resolve spontaneously within 7–14 days, despite continuous treatment. The occurrence of these adverse effects is readily understood from the physiological actions of somatostatin in the gastroenterological tract and exocrine pancreas (2, 3). The spontaneous resolution of these symptoms suggests rapid adaptation/desensitization/tachyphylaxis of the effects of octreotide on the function of the gastrointestinal tract and pancreas. Indeed, after 7 days of octreotide administration in healthy volunteers the initial dose-dependent inhibitory effects on the secretion of gastric acid, amylase, trypsin and lipase diminish and subsequently disappear completely (13, 14). Octreotide therapy can lead to changes in bile composition and gall bladder contractility (15). Up to one-third of patients with acromegaly develop biliary sludge or gallstones, but symptomatic gallbladder disease occurs in only 1% of patients per treatment year (12). Octreotide inhibits GH, insulin and glucagon secretion in normal individuals, while it delays the absorption of carbohydrates. In the first days of octreotide administration reduced glucose tolerance is observed. However, after 1 week adaptation develops, and during

long-term administration, octreotide does not change glucose homeostasis in normal individuals, while also GH secretion and IGF-I levels remain unchanged. An example of the rapid adaptation of the initial suppressive effect of octreotide on normal GH secretion in rats is shown in Fig. 2.

The rapid adaptation of these initial effects of octreotide on a number of physiological functions in different organ systems eventually resulted in disappointment concerning its potential clinical use for a number of gastrointestinal and pancreatic diseases and diabetes. The transient suppression by octreotide of pancreatic enzyme suppression turned out to be too short-lived to improve the outcome of elective pancreatic surgery or of pancreatic fistulas. Also in secretory diarrhea, intestinal fistulas, the metabolic control and the prevention of chronic complications of diabetes, in (neonatal) hypoglycemia, nesidioblastosis and in the prevention of tall stature, long-term therapy with octreotide failed or demonstrated only short (days) transient beneficial effects (12, 16).

Only in the initial treatment of acute variceal bleeding octreotide transiently lowers blood pressure in the abdominal vessels, improving the outcome in a subset of patients (17).

Acromegaly

The introduction of octreotide in the medical treatment of acromegaly has been of paramount benefit for the majority of patients: a marked relief of symptoms occurs rapidly after the start of therapy, for example headaches, excessive perspiration, paresthesias and carpal syndrome improve together with the overall quality of life (12, 18, 19). Also disease-associated co-morbidities including cardiac and respiratory disorders (snoring, sleep apnea) improve during long-term therapy.

There is evidence that an early diagnosis and normalization of GH/IGF-I levels improves the excess mortality risk associated with acromegaly (20, 21). However, it remains unknown to which extent medical therapy contributes to this.

The initially available subcutaneous form of octreotide reduced GH and IGF-I levels in most patients (18, 19, 22), but the monthly Octreotide-LAR preparation subsequently caused a similar or even better control (23). Interestingly, Octreotide-LAR and Lanreotide-Autogel elicited similar response rates (24, 25). From these studies, it became evident that GH was controlled in 57%, and IGF-I normalized in 67% of patients.

Figure 2

The effect of twice daily subcutaneous administration of octreotide (SMS 201-995) or placebo for 4 (left panel), 6 (middle panel) or 10 days (right panel) on circulating GH levels in normal female rats. Blood was collected 30 min after the last injection; $n = 8$ animals per group; values represent mean $\pm$ S.E.M. Adapted from Ref. (52).

However, these biochemical response rates showed considerable variation between studies. Colao *et al.* (26) observed response rates varying between 17 and 86% for Octreotide-LAR. A multitude of factors might contribute to these variations: difference in patient populations with regard to tumor size, age, inclusion of treatment responders and pretreatment with medical therapy are potential confounders. Another problem is that biochemical targets vary between studies, that the standardization of GH and IGF-I assays is often lacking, but most important that over the past years biochemical endpoints have become more strict in their requirement of age-adjusted normalization of both mean GH and IGF-I levels (27). In prospective studies using stringent composite biochemical endpoints to evaluate treatment-naïve patients not preselected for responsiveness to prior somatostatin therapy, response rates are ranging from 17 to 37%.

Other effects of somatostatin analog therapy in acromegaly are also of clinical importance: tumor shrinkage occurs in two-third of patients (27). Tumor volume reduction is observed typically within 3 months, reaching its maximal after 6–12 months, and lasts throughout therapy. During treatment (remnant) anterior and posterior pituitary function remains intact.

Escapes from octreotide therapy are extremely rare: once the GH-secreting pituitary adenoma initially responds with a decrease in GH release and tumor shrinkage one can rely on the maintenance of this effect in the long-term follow-up. Stopping octreotide therapy results in most instances in a slow reversal of GH release, symptomatology and tumor size. This reversal can take many months. In a limited number of patients a biochemical ‘cure’ has been observed in the long-term follow-up after stopping somatostatin analog treatment. The mechanism of this phenomenon remains unclear. Spontaneous hemorrhage within the tumor tissue might have happened somewhere in the course of the disease.

Pathophysiological explanation of the effects of octreotide came mostly from *in vitro* studies with tumor tissue removed from acromegalic patients during transsphenoidal surgery (9, 28): the number of SST2 on the GH-secreting pituitary adenoma cells are closely related to the *in vivo* response of GH and IGF-I levels to octreotide (29, 30). Low SST2-expressing tumors exhibit a poor response (Fig. 3). SST2 receptor expression appears not the only determinant in the response to octreotide treatment. Other factors, including cellular E-cadherin, beta-arrestin 1 and filamin-A, have been associated with

Figure 3

Patients that achieved IGF-1 normalization after adjuvant treatment with long-acting octreotide (Octreotide-LAR) showed significantly higher SST2A immunoreactivity (as quantified by an immunoreactivity score (IRS)) compared with the non-normalized group ($P = 0.002$; $n = 18$). Adapted from Ref. (29).

response to treatment with octreotide and lanreotide (31, 32, 33). The mechanism of action of octreotide on these pituitary adenomas involves not only an acute suppressive effect on GH secretion, but eventually hormone synthesis may decrease. Somatostatin does not seem to have an inhibitory effect on GH mRNA expression in primary cultures of human GH-secreting pituitary adenomas (34). On the other hand, GH mRNA levels are significantly lower in adenomas of acromegalic patients treated with octreotide, compared to adenomas of octreotide-naïve patients (35). Moreover, inhibition of GH release in somatotroph adenomas by octreotide is associated with accumulation of lysosomes, which suggests that octreotide induces increased lysosomal degradation of stored hormone (36). Altogether, this results into shrinkage of the GH-synthesizing and storing capacity and of related intracellular components. This shrinking effect does probably not include an important anti-tumor effect, as reflected in rebound GH secretion and reversal of tumor size after stopping octreotide administration. The mechanism which ascertains the long-term effect of octreotide on GH secretion and tumor size without an escape/adaptation/desensitization/tachyphylaxis could involve a difference in the internalization and reappearance of the peptide receptor complex on the cell membrane and/or a difference in intracellular mechanisms involved in desensitization processes, between the adenoma cell and SST2 on normal target organs (9).

TSH-secreting pituitary adenomas

Most TSH-secreting pituitary adenomas express SST2 and respond to octreotide with suppression of hormone release and control of tumor growth, as well as clinical improvement (37, 38).

Gastro-entero and pancreatic neuroendocrine tumors

Gastro-entero and pancreatic neuroendocrine tumors (GEP-NETs) have retained many characteristics of the neuroendocrine cells in the gut and endocrine pancreas from which they originate: more than 80% of these tumors express SST2 (39, 40). Most are slow-growing malignant tumors, which have metastasized at diagnosis. Their clinical manifestations are often related to hormonal hypersecretion.

Octreotide controls diarrhea and flushing attacks caused by an overproduction of serotonin and tachykinins in 70–90% of carcinoid patients (41), while it ameliorates dehydration, hypokalemic alkalosis, diarrhea, peptic ulceration, hypoglycemic attacks and necrolytic skin lesions in 50–80% of patients with endocrine pancreatic tumors secreting vasoactive intestinal polypeptide, gastrin, insulin and glucagon, respectively (12, 42). The immediate clinical effects of somatostatin analog therapy on quality of life are in most cases striking.

From early on after the clinical introduction of octreotide in the mid-eighties there have been suggestions that this medical treatment might prolong survival of patients with GEP-NETs. Such an effect might be attributed on the one hand to the clinical improvement in many of these patients during control of hormonal hypersecretion. On the other hand, there were many experimental studies, mainly from Schally's group suggesting direct anti-tumor effects by somatostatin analog administration (43, 44).

Two large clinical trials indeed demonstrated a direct anti-tumor effect of Octreotide-LAR (PROMID study) and Lanreotide-Autogel (Clarinet study) in patients with well-differentiated metastatic GEP-NETs (45, 46): in the first study octreotide administration delayed tumor progression from 6 to 14.3 months, while in the other study lanreotide induced after 2 years a median progression-free survival of 65.1 vs 33.0% in the placebo group. In these studies, progression of tumor growth was measured, while potential shrinkage in a subset of patients was not reported.

The molecular basis of the anti-proliferative effect of octreotide/lanreotide in GEP-NETs suggests that their interaction with SST2 on the tumor cells is coupled to intracellular signaling pathways that directly or indirectly influence cell cycling (47), apoptosis (48) and/or angiogenesis (49).

The immediate clinical improvement together with the proven anti-tumor effects of somatostatin analog therapy in metastatic, inoperable GEP-NETs make these patients, if SST2 are present on these tumors (vide infra), candidates for long-term primary treatment with octreotide/lanreotide.

A major problem of somatostatin analog therapy in these patients is, however, that eventually a decrease/loss of the control of hormonal secretion and of tumor growth develops (50, 51). It can initially be reversed by increase of the dose of octreotide/lanreotide. Escape from therapy seems not related to transient downregulation of SST2 on the tumor cells, because sensitivity is not restored after a drug holiday (52). This loss of sensitivity seems initially be related to a loss of connection between the peptide receptor complex and its intracellular messenger system, but eventually tumor cell clones appear that lack SST2 (9).

In vivo visualization of SST2 receptors

The presence of a high density of SST2 receptors on human neuroendocrine tumors, as demonstrated by *in vitro* autoradiography using ^{125}I -Tyr3-octreotide (39, 40), as well as the inhibitory effect of octreotide on hormone secretion by these tumors, suggested the feasibility to visualize such tumors *in vivo* in patients after the administration of Tyr3-octreotide coupled to ^{123}I (53). [^{123}I -Tyr³]octreotide scanning revealed the localization of the primary tumors and their metastases in 38 of 42 patients with carcinoids, islet cell tumors and paragangliomas (54). The surgically removed tumors of a number of these patients were subsequently investigated *in vitro*, while also preoperative hormonal studies with octreotide had been carried out. There was a close parallel relationship between the presence of SST2 on these tumors *in vitro*, the hormonal response pre-operatively, and the *in vivo* visualization of these tumors (55). Because of logistical and practical drawbacks of the use of ^{123}I , an alternative was created by coupling a spacer (DTPA (diethylenetriaminepentaacetic acid)) to octreotide, resulting in a compound which efficiently binds to ^{111}In (56).

The introduction of ^{111}In -DTPA-octreotide scintigraphy in patients with GEP-NETs has revolutionized their diagnostic and therapeutic approach (53, 54, 55, 57, 58): 80–100% of GEP-NETs express at diagnosis SST2, allowing the visualization of the primary tumor, as well as previously unknown metastases. SST imaging has greater sensitivity than conventional imaging studies in 60–90% of patients. Whole body imaging at one time for the detection of distant metastases resulted in management changes in 25–50% of cases. SST scintigraphy allows visualization of GEP-NET lesions smaller than 1 cm in 50% of cases, but results heavily depend on the degree of differentiation, because poorly differentiated tumors frequently either do not express SST2 or do so in low densities. A positive SST scan predicts whether the patient is a candidate for SST2-targeted radiotherapy (vide infra). Recently with the introduction of PET imaging molecular imaging with ^{68}Ga -labeled somatostatin analogs has been developed; this new compound allows an even greater spatial resolution than ^{111}In -DTPA-octreotide (59).

The clinical introduction of SST scintigraphy has provided many new insights in the distribution of SST in human diseases (52, 54, 57). Apart from most GEP-NETs many other neuroendocrine tumors express enough SST to allow visualization of their primary location as well as their metastases: these include paragangliomas, pheochromocytomas, medullary thyroid cancers and small-cell lung cancers. A number of adenocarcinomas originating from the breast, kidney, colon, ovary and other organs, which contain dispersed neuroendocrine cells express SST2 at a variable degree, allowing their *in vivo* visualization. Tumors originating from other tissues that normally express SST like the leptomeninges (meningiomas), glia (well-differentiated astrocytomas), lymphocytes (malignant lymphomas) can be visualized as well. Finally, it was demonstrated that clusters of activated immune cells in granulomas (in sarcoidosis and tuberculosis and rheumatoid arthritis) can be visualized *in vivo* (52, 54, 57). Today, there is limited knowledge concerning the pathophysiological role of SST2 expression.

The visualization of SST on such a variety of disease processes was unexpected. It was proven that the sensitivity and specificity of SST imaging is extremely high: indeed in all conditions mentioned above the presence of SST on the visualized tissues was ascertained *in vitro*. However, one should realize that the specificity of SST imaging for GEP-NETs is not high: in a given patient one should remain alert whether a SST2-positive location indeed represents a GEP-NET, rather than for example a previously unknown meningioma, sarcoidosis or rheumatoid arthritis.

SST-targeted radiotherapy

Early studies demonstrated that exposure of cultured SST2-positive human tumor cells to [^{125}I -Tyr 3]octreotide resulted in a dose- and time-dependent specific uptake and retention of radioactivity within these tumor cells (Fig. 4) (60, 61). Also, in animal studies involving rats bearing SST2 expressing tumors, it was demonstrated that such internalization and retention occurs *in vivo*, while the unbound somatostatin ligand is rapidly cleared via the kidneys: this results in a high gradient between radioactivity in the blood and the tumor tissue (56).

The use of radiolabeled somatostatin analog therapy for the therapy of advanced well-differentiated GEP-NETs has been developed step by step over the past 25 years (62). Initially, efficacy results were based on the use of very high doses of ^{111}In -DTPA octreotide. More promising results were subsequently found with ^{90}Y -DOTA Tyr 3 -octreotide and ^{177}Lu -DOTA-Tyr 3 -octreotide. Eventually ^{177}Lu -DOTA-Tyr 3 -octreotate was found to be the compound with the highest affinity to SST2. Lutetium-177 is a beta- and gamma-emitting radionuclide with a maximum particle range of 2 mm, and a half-life of 160 h. In a multinational, multicenter study in 229 patients with well-differentiated metastatic midgut neuroendocrine tumors 113 patients received Octreotide-LAR alone (60 mg/month), and 116 patients received the same dose of Octreotide-LAR once a

month together with four infusions of [^{177}Lu -DOTA-Tyr 3] octreotate (7.4 GBq with intervals of 8 weeks). Treatment with the ^{177}Lu compound resulted in a longer progression-free survival: at 20 months 65 vs 10.8% in the high dose Octreotide-LAR only group, while there was also an increased overall survival (14 vs 26 deaths). Toxicity and adverse effects were limited (63). [^{177}Lu -DOTA, Tyr 3] octreotate therapy for NET patients recently received EMA and FDA approval.

Somatostatin receptor subtype 5 (SST5)

SST5 is distributed throughout the human body in several organs, including the anterior pituitary, the endocrine cells lining the gut and of the pancreas. In human pathology SST5 expression is found to be of clinical importance in both GH- and ACTH-secreting pituitary adenomas (64, 65), while their presence is low in GEP-NETS (65).

Pasireotide is a multireceptor-targeted somatostatin analog with an in comparison to octreotide slightly lower affinity to SST2, but a nearly 40 times higher affinity to SST5 (66). Corticotropinomas predominantly express SST5 (67, 68) and ACTH secretion by cultured tumor cells obtained at transsphenoidal operation is suppressed by pasireotide in nanomolar concentrations in 60% of cases (69). In a multicenter study pasireotide (600 μg (82 patients) or 900 μg (80 patients) twice daily) normalized urinary free cortisol concentrations in 15 and 25% of patients with Cushing's disease, respectively (70).

In early studies from Melmed's laboratory, it was demonstrated that SST5 expressed on GH-producing tumor cells were functional: several new chimeric compounds which bound with high affinity to both SST2 and SST5 suppressed GH more than SST2-specific compounds alone (6, 71).

Van der Hoek *et al.* (72) compared the effects of nanomolar concentrations of octreotide and pasireotide: in a number of acromegalic tumors a higher expression of SST 5 mRNA expression was accompanied by a significantly higher suppression of GH by pasireotide (Fig. 5). Indeed, as expected, a comparison between the effect of long-term treatment of Octreotide-LAR and pasireotide-LAR in acromegalic patients demonstrated that more patients were biochemically cured with pasireotide (73).

From pre-clinical data, it had become evident that pasireotide administration in young rats completely stops body growth, while IGF-I levels remain lowered during long-term follow-up (74). Also in a study by Feelders *et al.* (75) in patients with Cushing's disease, IGF-I levels

Figure 4

Time-dependent increased uptake of [^{125}I -Tyr 3]octreotide by cells of a human carcinoid. Values represent the amount of uptake, expressed as the percentage of the added dose of [^{125}I -Tyr 3]octreotide, in the absence and in the presence of excess (1 μM) unlabeled octreotide, to determine non-specific internalization. Adapted from Ref. (60).

Figure 5

In vitro data of two acromegalic patients, demonstrating a preferential inhibition of GH secretion *in vitro* by pasireotide in cultured cells with high SST5 expression, compared to SST2 expression (patient 12). Relative SST2 and SST5 expression in GH-secreting pituitary adenoma tissue of patient 6 (lower left) and patient 12 (lower right). Effects of octreotide (10 nM) and pasireotide (10 nM) on GH secretion by cultured pituitary adenoma cells from patient 6 (upper left) and patient 12 (upper right). Adapted from Ref. (72).

decreased over time during pasireotide administration, with a level below the lower limit of normal range in 9 of 17 patients after 80 days (75).

In all clinical studies reported so far pasireotide caused from the very first injection on a deterioration of glucose metabolism, which did not improve during continued administration of the drug. In about 40% of patients with Cushing's disease hyperglycemia was diagnosed during pasireotide treatment, while 18% developed diabetes, despite the expected improvement of glucose tolerance in response to the control of ACTH/cortisol hypersecretion (70). Pasireotide induces glucose intolerance and diabetes in about half of acromegalic patients; there are no guidelines so far concerning the question what the place of this drug is in comparison with octreotide/lanreotide alone or in combination with a GH receptor antagonist.

Octreotide after 40 years

Octreotide remains 40 years after its development a drug, which is commonly used in the treatment of acromegaly and GEP-NETs. Very little innovation that competes

with this drug occurred over this period. As mentioned earlier octreotide and lanreotide have a similar efficacy and safety profile. The long-acting depot preparations of both drugs can be interchanged in the clinic. Only an oral formulation of octreotide is on the horizon for clinical introduction (76). The rapid adaptation of SST2 on normal organs makes the drug very safe and well tolerated. In acromegaly octreotide rapidly improves symptomatology and quality of life, it shrinks pituitary tumor size in two-third of cases without growth during long-term follow-up; also pituitary function remains intact, while no escape from therapy occurs. The number of patients in which octreotide eventually induces a biochemical cure depends on how strict composite endpoints are defined. Addition of once daily or weekly injections of a GH receptor antagonist is successful in most cases (77). For patients with GEP-NETs the introduction of octreotide meant an enormous improvement in their quality of life. Apart from control of hormonal hypersecretion somatostatin analogs were proven to have anti-proliferative effects as well, as demonstrated by delay in tumor growth progression, as well as survival. Although not reported in detail, a number of acromegalic patients are currently treated for more than 25 years with continuing efficacy and without notable adverse effects.

SST2 visualization and SST2-targeted radiotherapy revolutionized diagnosis and treatment of GEP-NET patients: the scan indicates the localization of the primary tumor, as well as their often previously unknown metastases, while a positive scan predicts sensitivity of the tumor tissue to octreotide: this applies both to the treatment with 'cold' somatostatin analogs (hormonal hypersecretion and control of tumor growth), as to the use of SST2-targeted radiotherapy (proven shrinkage and prolonged survival as well). The central problem to be solved in patients with GEP-NETs is how to optimally use the window of opportunity of SST2 expression on the tumors: during long-term therapy with octreotide eventually loss of sensitivity occurs with an escape from treatment. This escape is related to loss of tumor differentiation and eventually loss of SST2 expression. It is crucial to define in a given patient the optimal moment for SST2-targeted radiotherapy. Moreover, depending on the tumor type, 10–50% of NET patients have tumors that do not express sufficient SST to make them eligible for SST2-targeted radiotherapy (78). Preliminary studies suggest that pharmacologically driven transient upregulation of SST2 to enhance the effect of targeted radiotherapy will be a feasible option in some patients (79). SST-targeted radiotherapy is an innovative

Review	S W J Lamberts and L J Hofland	Octreotide	181:5	R180
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viable development in clinical medicine. Based on this development a new research field, called theranostics (80), is developing in Nuclear Medicine, with ^{177}Lu -PSMA (prostate-specific membrane antigen) administration as an innovative successful treatment for androgen-receptor-resistant prostate cancer patients (81). SST5 physiology turned out to be different from SST2: pasireotide, a compound with a 40 times higher affinity for SST5 than octreotide causes in normal individuals GH/IGF-I deficiency, as well as clinically significant impairment of glucose metabolism. In contrast to SST2, SST5 activation in normal organs appears not to adapt/desensitize. These adverse effects limit its use in acromegaly and in Cushing's disease considerably. Guillemin (7) commented in his Nobel lecture on the limitations of the clinical use of somatostatin: he was right with regard to SST5: the adverse effects on normal organs limit the use of SST5-specific analogs. However, SST2 desensitization on normal organs, which develops within several days, opened the opportunity for octreotide to be administered for a prolonged time without important adverse effects.

Declaration of interest

L H has received investigator-initiated research support from Ipsen and Novartis Pharma. S W J L has nothing to disclose.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 14 February 2019

Revised version received 29 July 2019

Accepted 9 August 2019