

Review

From somatostatin to octreotide LAR: evolution of a somatostatin analogue

Lowell Anthony

Louisiana State University, New Orleans, LA, USA

Pamela U. Freda

Columbia University, New York, NY, USA

Address for correspondence:

Lowell Anthony, MD, Division of Hematology/
Oncology, Louisiana State University, New Orleans,
LA, USA.

Tel.: +1 504 568 5722; Fax: +1 504 464 8525;
lantho@lsuhsc.edu

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Abstract

Background:

Acromegaly is characterized by overproduction of growth hormone (GH) by the pituitary gland. GH stimulates the synthesis of insulin-like growth factor-I (IGF-I), and the somatic growth and metabolic dysfunction that characterize acromegaly are a consequence of elevated GH and IGF-I levels. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rare, slow-growing neoplasms that have usually metastasized by the time of diagnosis. The majority of GEP-NETs are carcinoid tumors whose syndrome is caused by the hypersecretion of biogenic amines, peptides and polypeptides responsible for the principal symptoms of diarrhea and flushing.

Methods:

The MEDLINE and EMBASE databases were searched for preclinical and clinical studies of octreotide (Sandostatin*), a potent synthetic somatostatin analogue, in patients with acromegaly or GEP-NETs.

Objective:

This article reviews the 20 years of clinical experience with octreotide and the impact it has made in patients with acromegaly or GEP-NETs.

Results:

Octreotide has proven to be an essential component in the management strategy of acromegaly and GEP-NETs over the past 20 years. The multiple beneficial effects of octreotide throughout the body, combined with its established safety profile (the most common adverse effects are injection-site pain and gastrointestinal events), have made it an appealing option for clinicians. The advent of the long-acting release (LAR) formulation of octreotide provided additional benefits to patients through monthly administration, while maintaining the efficacy and tolerability profile of the daily subcutaneous formulation.

Conclusions:

Octreotide is a potent synthetic somatostatin analogue that has become the mainstay of medical therapy for tumor control in neuroendocrine disorders such as acromegaly and GEP-NETs. The development of octreotide LAR offered a further advancement; less frequent dosing provided valuable benefits in quality of life to patients, with equivalent efficacy and tolerability. Moreover, recent results from the PROMID study have confirmed the antiproliferative effect of octreotide LAR in patients with well-differentiated metastatic GEP-NETs of the midgut. New therapeutic uses of octreotide are currently under investigation in a variety of clinical settings.

Introduction

Since its development 20 years ago, octreotide (Sandostatin*), a potent synthetic somatostatin analogue, has emerged as the foremost medical therapy for

*Novartis Pharma AG, Basel, Switzerland.

endocrine disorders such as acromegaly and carcinoid syndrome associated with gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Before the introduction of octreotide, the negative impact of these rare hormonal disorders on patients' quality of life was considerable, and treatment options beyond surgery were limited¹⁻³. The development of subcutaneous octreotide, and later its long-acting release (LAR) formulation, represented major clinical breakthroughs. With octreotide therapy, excessive hormone secretion could be controlled effectively, resulting in a substantial improvement in quality of life for patients^{1,2}.

Acromegaly is a rare, chronic hormonal disorder characterized by overproduction of growth hormone (GH) by the pituitary gland, which in turn results in excessive production of insulin-like growth factor-I (IGF-I) in the liver^{4,5}. In >90% of cases, GH hypersecretion is caused by a benign GH-secreting pituitary adenoma⁶. Acromegaly not only increases patients' risk of severe comorbidities, including diabetes mellitus, hypertension and cardiovascular disease, but patients often suffer from physical deformities, such as enlarged hands and feet, frontal bone bossing and coarse facial features^{1,3,5}. Patients with active acromegaly also have a two- to three-fold increased mortality risk⁷. Until the 1980s, surgery, radiation therapy and dopamine agonists were the only treatments available to patients with acromegaly⁸. As many tumors were too large or invasive to be completely resected, only a minority of patients could be cured with surgery alone⁸. As dopamine agonists are minimally effective and radiation therapy takes many years to normalize hormone levels, disease in these patients remained uncontrolled for years. The introduction of octreotide in the early 1980s changed the course of acromegaly treatment, and the disease became controllable in two-thirds of patients^{8,9}.

The treatment of patients with GEP-NETs, in particular those suffering from carcinoid syndrome, was also substantially advanced upon the introduction of octreotide^{9,10}. GEP-NETs are rare neoplasms that originate from neuroendocrine cells in the digestive tract, pancreas, lungs and liver¹¹. GEP-NETs are characterized by the production and secretion of excessive amounts of peptide hormones and biogenic amines that are normally regulated in the body in smaller amounts¹¹. Due to the indolent nature of GEP-NETs, patients may be asymptomatic for years or present with only vague symptoms of abdominal pain which are often confused with other disorders such as irritable bowel syndrome. As such, treatment is often considered only when well-differentiated nonpancreatic GEP-NETs (often referred to as carcinoid tumors), the most common type of GEP-NETs, metastasize to the liver, and the clinical manifestations of carcinoid syndrome develop, resulting in more severe symptoms of flushing, debilitating diarrhea, and cramping in the lower abdomen^{10,12}. Although a number of therapeutic

strategies, including chemotherapy, radiotherapy and surgery, have been historically utilized in the management of GEP-NETs, the overall clinical results were disappointing until the development of octreotide². By inhibiting hormonal hypersecretion of GEP-NETs, octreotide reduces circulating hormone levels, stabilizes tumor growth and significantly ameliorates symptoms in patients^{10,12}. Moreover, the introduction of octreotide LAR has led to a substantial improvement in survival in patients with GEP-NETs¹³.

Octreotide is the most prescribed and most studied somatostatin analogue for acromegaly and GEP-NETs. Its development is considered a milestone in the treatment of patients with these rare, serious hormonal disorders. This article reflects on the 20 years of clinical experience with octreotide and its impact on quality of life in patients with acromegaly and GEP-NETs, beginning with its development in the early 1980s to the launch of a long-acting formulation in 1997. Future therapeutic applications for octreotide are continuing to grow and will be discussed.

MEDLINE and EMBASE were searched using the terms 'Sandostatin', 'octreotide', 'Somatuline', 'lanreotide', 'acromegaly', 'neuroendocrine tumors', and 'NETs'. Searches were performed for publications from January 1 1980 to July 13 2009. When available, large, well-controlled trials with appropriate statistical methodology were preferred.

Development of octreotide

The discovery of somatostatin in 1973, for which Roger Guillemin and Andrew Schally shared the Nobel Prize, provided a new approach to investigating disease states associated with endocrine hypersecretion such as acromegaly and GEP-NETs^{14,15}. Somatostatin is an inhibitory hormone that is widely distributed throughout the central nervous system (CNS) and peripheral tissues. Native somatostatin plays an important regulatory role in neurotransmission and secretion, preventing the release of GH, thyroid-stimulating hormone, GI hormones, pancreatic enzymes and neuropeptides^{14,15}. The rate of gastric emptying, smooth muscle contractions and blood flow within the intestine are also modulated by somatostatin.

Endogenous somatostatin exerts its biological effects via activation of somatostatin receptors expressed in the CNS, hypothalamus, GI tract and pancreas¹⁴⁻¹⁶. Five somatostatin receptor subtypes (sst₁₋₅), each with distinct signaling pathways and tissue distribution, have been identified, cloned and characterized with respect to binding properties¹⁴⁻¹⁶. Pituitary tumors found in patients with acromegaly mainly express sst₂ and sst₅, while GEP-NETs express multiple sst, although predominantly sst₂¹⁴. When it became apparent that the pharmacological properties of native somatostatin limited its use in clinical

Table 1. IC₅₀ values of native somatostatin and octreotide for the different somatostatin receptor subtypes. Adapted from Hofland and Lamberts 2003¹⁴.

	sst ₁	sst ₂	sst ₃	sst ₄	sst ₅
Somatostatin, nmol/L	2.3	0.2	1.4	1.8	0.9
Octreotide, nmol/L	>1000	0.6	34.5	>1000	7

sst; somatostatin receptor subtype.

practice, the search began for analogues of somatostatin to provide a more clinically useful molecule with strong affinities for selected receptor subtypes.

Octreotide is a synthetic octapeptide analogue of somatostatin with more prolonged pharmacological actions than the endogenous hormone. Native somatostatin has a half-life of 2–3 minutes; octreotide has a half-life of 90–120 minutes when administered subcutaneously, and a pharmacodynamic action lasting up to 8–12 hours^{15,17}. Moreover, octreotide selectively binds to sst₂ and to a lesser extent sst₅ (Table 1), providing a high ratio of therapeutic benefit over adverse effects^{9,14,15,17}. In the pituitary gland, octreotide has an approximately 40-fold greater potency than native somatostatin in inhibiting GH secretion^{15,18}. In the pancreas, octreotide has been shown to inhibit insulin, glucagon, pancreatic polypeptides and bicarbonate secretion. The pharmacological actions of octreotide in the GI tract are numerous, and include inhibition of gastrin, motilin, secretin and vasoactive intestinal polypeptides, as well as decreased blood flow to the gut, intestinal motility and carbohydrate absorption. Octreotide also increases water and electrolyte absorption in the GI tract, which is essential in the treatment of GEP-NETS^{15,18}. Importantly, treatment with octreotide does not result in rebound hypersecretion of hormones.

The development of the long-acting release (LAR) formulation of octreotide in 1997 further improved the clinical application of this compound. Octreotide LAR is a long-acting release formulation in which octreotide is encapsulated in microspheres of a slowly dissolving polymer, providing a predictable pharmacokinetic profile and steady-state kinetics when administered intramuscularly once every 28 days¹⁹. The pharmacokinetic profile of octreotide after a single dose of octreotide LAR 20 mg exhibits three distinct phases: following a transient increase in concentration after administration on day 1, there is a lag phase for about 5 days, during which octreotide concentrations decrease, followed by a new increase in drug levels and a plateau phase for about 30 days¹⁹. Octreotide LAR retains the pharmacological characteristics of subcutaneous octreotide, and reaches steady-state concentrations within three injections²⁰. The short-acting formulation is rarely used for long-term therapy, but can be particularly effective for control of headaches in some

patients with acromegaly, and for use as 'rescue' therapy in patients with carcinoid syndrome.

Clinical experience with octreotide

Acromegaly

The goals of treatment for patients with acromegaly include controlling hormone hypersecretion from the tumor, normalizing circulating GH and IGF-I levels, controlling tumor growth whilst preserving normal pituitary function, and controlling or eliminating comorbidities and symptoms^{21,22}. The use of octreotide in the treatment of acromegaly is supported by more than 20 years of clinical research and experience.

Octreotide is typically used as a post-operative therapy to control GH secretion after debulking a tumor or as first-line therapy for patients who are unsuitable for neurosurgery (Figure 1)^{21,22}. Since the pharmacological properties of octreotide were first described in 1982 by Bauer *et al.*⁹, clinical evaluation has consistently demonstrated that both the subcutaneous and long-acting release formulations of octreotide effectively control GH and IGF-I levels and reduce the incidence of comorbid symptoms in most patients with acromegaly. Early studies of subcutaneous octreotide showed that up to 90% of patients with acromegaly experienced some fall in GH and IGF-I serum levels during treatment with octreotide²³. Longer-term studies (up to 4 years) published in the 1990s demonstrated that subcutaneous octreotide maintains GH suppression ($\leq 5 \mu\text{g/L}$) and normalizes IGF-I levels in up to 65% and 68% of patients with acromegaly, respectively, with no reported tachyphylaxis^{23–25}.

Octreotide LAR offers the convenience of once-monthly administration compared with daily subcutaneous drug administration. The efficacy profile of octreotide LAR was quickly established as similar to that of subcutaneous octreotide in patients with acromegaly, with the potential for improved patient compliance²⁶. Several long-term studies of octreotide LAR (up to 9 years) have demonstrated that around 70% of patients achieve GH levels $\leq 2.5 \mu\text{g/L}$ and up to 75% of patients achieve age-matched normalized IGF-I levels^{27–29}. Results from a recent meta-analysis of octreotide LAR in 44 trials that enrolled over 600 patients show that octreotide controls GH and IGF-I in 57% and 67% of patients, respectively³⁰. Interestingly, this meta-analysis also compared the efficacy of octreotide LAR in patients who were and were not preselected for therapy based on responsiveness to octreotide. Preselection did not influence GH normalization rate, but was a positive predictor of IGF-I normalization (Figure 2)³⁰. Importantly, no tachyphylaxis has been reported in the treatment of patients with acromegaly

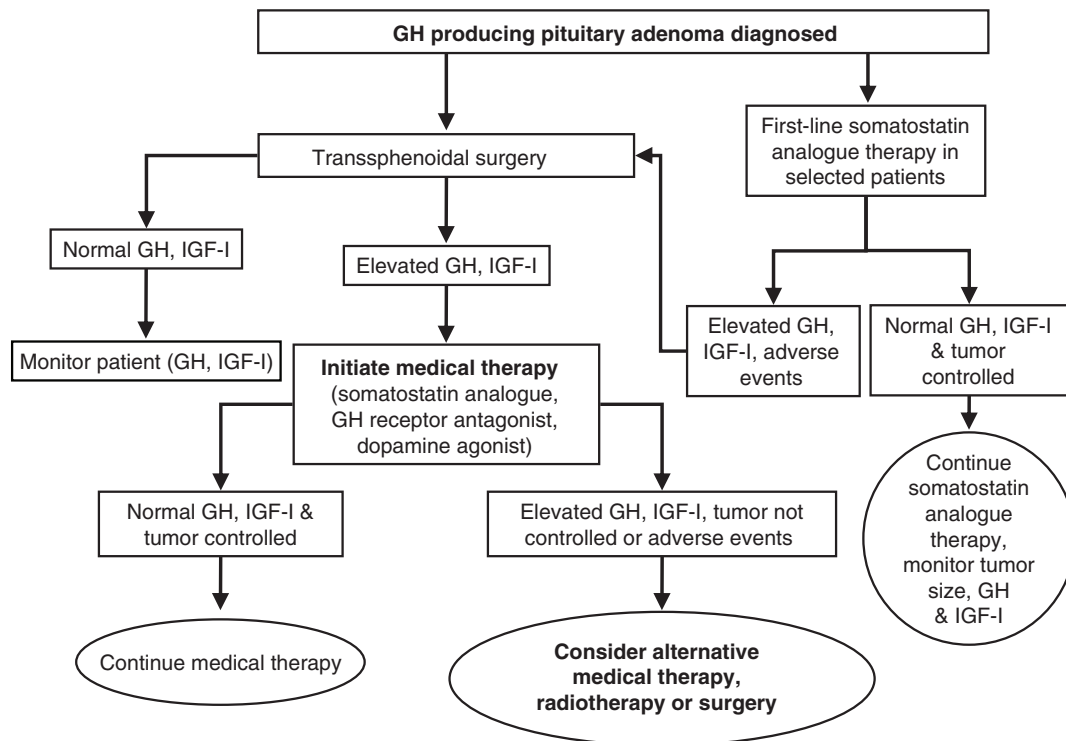
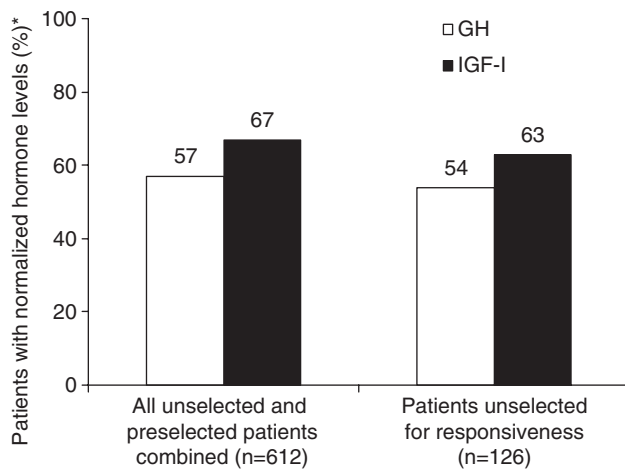


Figure 1. Acromegaly treatment algorithm.



*GH $\leq 2.5\text{--}5 \mu\text{g/L}$ and normalized IGF-I for age/sex-matched controls

Figure 2. Octreotide LAR suppresses GH and IGF-I levels in patients with acromegaly (Freda *et al.* 2005).

over the long term (≥ 10 years) for either formulation of octreotide¹⁵.

Although there have been no large head-to-head studies comparing octreotide LAR with lanreotide Autogel, the only other long-acting somatostatin analogue available for the treatment of acromegaly, several small studies, most of which switched patients well-controlled on octreotide LAR therapy to treatment with lanreotide Autogel, have

shown that lanreotide Autogel is noninferior to octreotide LAR with regards to biochemical control³¹.

Octreotide markedly reduces the clinical symptoms of acromegaly, including debilitating headaches, amount of perspiration, paresthesia, fatigue, joint pain and carpal tunnel syndrome in 70% of patients with acromegaly^{23–25,27–29}. Even if biochemical control is not achieved, results from several studies show that symptomatic improvement occurs in most patients with acromegaly treated with octreotide. Long-term treatment with octreotide also improves cardiac performance in patients with normalized GH and IGF-I levels^{32,33}, although whether or not octreotide improves cardiovascular mortality is yet to be demonstrated.

In selected patients, such as elderly patients or those in whom the surgical risk is high, first-line medical therapy with octreotide LAR should be strongly considered. There is some evidence to suggest that first-line medical therapy should also be favored in patients with macroadenomas without visual or neurological compromise, but for whom the chance of surgical cure is low (Figure 1)^{28,34,35}. A recent study suggested that the biochemical control achieved with first-line octreotide LAR therapy is similar to that expected for surgical therapy²⁸. In this 9-year, long-term study in 67 patients with acromegaly who received octreotide LAR as first-line therapy, control of GH and IGF-I levels was achieved in 68.7% and 70.1% of patients, respectively. Tumor shrinkage occurred in 82.1% of patients, with an average reduction in tumor volume

of 62%. Furthermore, the percentage of patients achieving biochemical control and tumor shrinkage increased with time²⁸. Another recent study that randomized newly diagnosed patients with acromegaly to surgery or octreotide LAR showed that the 48-week treatment outcome seen with octreotide LAR was not statistically significantly different from that seen in patients who underwent surgery³⁵.

There are other data to suggest that surgical debulking prior to somatostatin analogue use improves efficacy^{36,37}. There is also debate as to whether preoperative octreotide use improves surgical outcome. Although some studies have not shown a benefit to long-term outcome with preoperative octreotide therapy^{38–40}, two studies have shown improved post-operative cure rates in patients with macroadenomas pretreated for 3–6 months with octreotide sc⁴¹ or octreotide LAR⁴². Finally, 3–6 months of preoperative octreotide may be useful in improving patients' clinical status prior to surgery, in terms of cardiac function, blood pressure, and glucose and lipid metabolism, thus facilitating anesthetic and surgical management⁴¹.

The use of first-line medical therapy should be considered on an individual patient basis. The surgical risks for the patient, the experience of the surgeon available, the tumor size and location, and patient preference should be taken into account. Failure to debulk a large tumor that is found to be incompletely somatostatin analogue responsive may limit additional options for therapy, such as radiotherapy or GH receptor antagonist therapy, due to tumor location and size constraints. Even some small tumors that clearly cannot be removed because of their location (such as in the cavernous sinus) are candidates for first-line medical therapy.

In patients receiving long-term octreotide LAR and who have well-controlled disease, individual tailoring of the dose, for example a reduction in the dose or an extension of the interval between doses to more than 4 weeks, may be considered in order to provide maximal benefit to the patient while maintaining adequate disease control^{43–45}. Furthermore, Ronchi *et al.* recently showed that somatostatin analogues may be successfully withdrawn in a subset of patients who respond well to treatment⁴⁶. Regular biochemical monitoring and neuro-radiological imaging is mandatory in patients with acromegaly withdrawn from medical therapy.

The costs of different medical therapies for acromegaly varies depending on the treatment, for example dopamine agonists (cabergoline), somatostatin analogues (octreotide LAR, lanreotide Autogel) and growth hormone antagonists (pegvisomant), the country and the method of healthcare payment. It is important to consider cost effectiveness and cost benefit in the treatment of patients with acromegaly, and these considerations require therapy to be individualized²². To date, there have been no reported cost-effectiveness studies comparing the different medical treatments available for acromegaly. Although the costs of

medical therapy for acromegaly are relatively high and some treatments are more expensive than others, these costs may be acceptable because the overall disease burden on the health system is low due to the rarity of acromegaly. Furthermore, determination of the cost/benefit ratio needs to include the consequences of long-term outcomes of poor disease control, as well as the occurrence of subsequent complications²².

GEP-NETs

Although surgery is considered the first-line therapy for patients with GEP-NETs, a cure is not possible in 80% of cases as most patients present at the advanced disease stage⁴⁷. Surgical debulking can reduce the extent of hormone production and relieve symptoms, but because the disease course of carcinoid tumors is often long, palliative care to maintain quality of life is particularly important (Figure 3). Relief from diarrhea and flushing, as well as biochemical control, are fundamental to improving quality of life in patients with symptoms of functioning GEP-NETs.

Octreotide was among the first biotherapeutic agents used in the management of GEP-NETs and continues to be a mainstay of therapy today, although it is rarely curative². In a review by Modlin *et al.* (2006), pooled data from more than 14 trials spanning the past two decades and including almost 400 patients revealed that 71% of patients with GEP-NETs experience resolution or improvement of diarrhea (range: 40–88%) and flushing (range: 48–100%) during treatment with octreotide². Diarrhea is the primary reason for patients to seek medical help, making effective long-term treatment essential. Biochemical responses to octreotide were seen in up to 77% of patients with GEP-NETs, demonstrating that octreotide effectively inhibits hormonal hypersecretion. Octreotide also has antiproliferative activity; although objective tumor responses are uncommon, 55% (range: 48–75%) of patients experience stable disease with octreotide therapy².

The effects of octreotide LAR have been evaluated in a study of 93 patients with carcinoid tumors and a confirmed diagnosis of carcinoid syndrome⁴⁸. Suppressing 5-HIAA levels, a metabolite of serotonin, is key for assessing and managing patients with carcinoid syndrome. Octreotide LAR rapidly reduces 5-HIAA levels by up to 50% in patients with carcinoid syndrome⁴⁸. Uncontrolled diarrhea due to carcinoid syndrome leaves patients at risk of serious comorbidities such as opportunistic intestinal infections and dehydration. By working at the site of carcinoid tumors, octreotide reduces bioactive secretions and reduces diarrhea frequency by 42% in patients with carcinoid syndrome (Figure 4)⁴⁸. The precise mechanisms by which octreotide exerts its effects on the GI tract in patients with GEP-NETs have not been completely

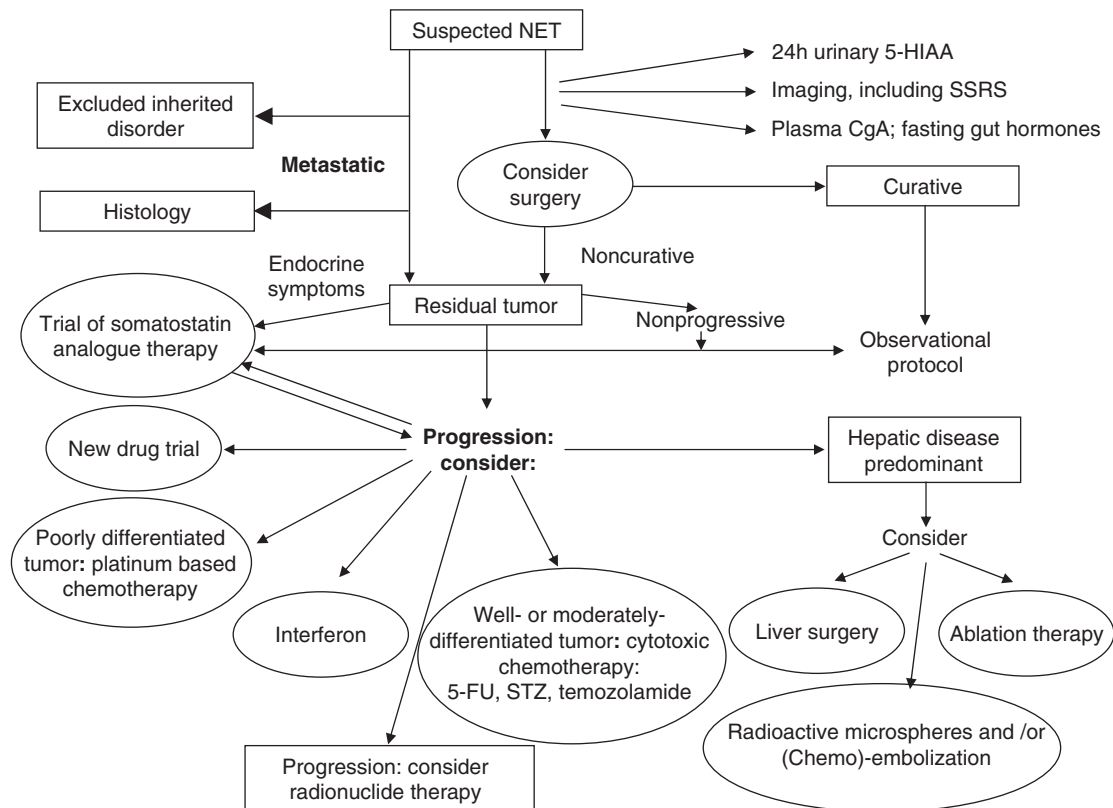


Figure 3. Algorithm for the investigation and management of NET. Reproduced from Ramage JK *et al.* Gut 2005;54(Suppl 4):iv116, with permission.

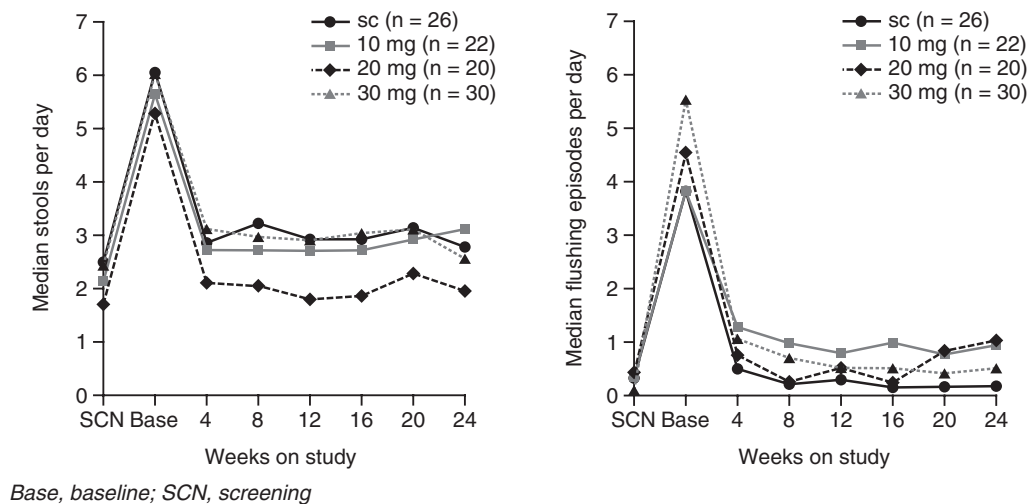


Figure 4. Octreotide LAR for control of diarrhea and flushing in patients with confirmed carcinoid syndrome. Reproduced from Rubin J *et al.* J Clin Oncol 1999;17:600–6, with permission.

elucidated, but in addition to controlling diarrhea and reducing secretions, octreotide promotes water and electrolyte absorption, decreases splanchnic blood flow and prolongs GI transit time^{48–50}. Flushing episodes in patients with carcinoid syndrome are also reduced by 84%, from 4.5 episodes/day to 0.7 episodes/day (Figure 4)⁴⁸.

Interestingly, octreotide LAR appears to improve survival in patients with carcinoid syndrome. In a retrospective analysis, survival was compared in 145 patients with carcinoid syndrome who were receiving octreotide LAR to 90 patients who had received subcutaneous octreotide¹³. Baseline characteristics were similar between the

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two groups. Survival in the octreotide LAR group was significantly higher: 229 months compared with 143 months in the control group ($p < 0.0001$)¹³. Thus, patients with carcinoid syndrome who received treatment with octreotide LAR had a 66% lower risk of death than patients receiving therapy with subcutaneous octreotide in this study¹³.

Octreotide LAR has also recently been evaluated as first-line therapy in difficult-to-treat nonfunctioning GEP-NETs. Approximately 40% of nonfunctioning pancreatic endocrine carcinomas cannot be cured by surgery because of advanced-stage disease. In a prospective phase IV study, 21 patients with advanced-stage, well-differentiated nonfunctioning pancreatic endocrine carcinomas were treated with octreotide LAR 20 mg. At a median follow-up of 49.5 months, eight (38%) patients had stable disease⁵¹. Thirteen patients (62%) experienced progressive disease after a median of 18 months. Notably, tumor progression correlated with a proliferative index (Ki-67) $\geq 5\%$ ($p = 0.016$), weight loss ($p = 0.006$) and absence of abdominal pain ($p = 0.003$) at diagnosis. Thus, treatment with octreotide LAR was associated with stabilization of disease and a better quality of life in 38% of patients⁵¹.

Recently, the antiproliferative effect of octreotide LAR has been demonstrated in a randomized, double-blind, placebo-controlled phase IIIb study (PROMID trial) in 85 patients with functioning or nonfunctioning metastatic GEP-NETs of the midgut⁵². At the time of the preplanned confirmatory interim analysis after 67 tumor progressions, octreotide LAR 30 mg/28 days led to a significant increase in time to tumor progression (TTP) compared with placebo (14.3 vs. 6.0 months; $p = 0.000072$), regardless of whether patients had a functioning or nonfunctioning tumor^{52,53}. A further *ad hoc* analysis performed 11 months later once all patients had been unblinded from treatment showed a further improvement in TTP with octreotide therapy versus placebo (15.6 vs. 5.9 months; $p = 0.000017$)^{52,54}. Patients with nonfunctioning tumors ($n = 52$) achieved a TTP of 27.14 months with octreotide LAR versus 7.21 months with placebo ($p = 0.0008$)⁵⁴. Octreotide LAR also significantly extended TTP in patients with functioning tumors ($n = 33$) compared with placebo (10.35 months vs. 5.45 months; $p = 0.0007$)⁵⁴.

In response to results from the PROMID study, guidelines from the National Comprehensive Cancer Network (NCCN) have been updated to recommend octreotide LAR 20–30 mg as a management option in patients with recurrent or unresectable metastatic carcinoid tumors originating from any primary site of disease (small bowel, colon, rectum, appendix, lung, thymus, stomach) irrespective of functional status, symptomatology and progression status⁵⁵.

There are fewer data available for lanreotide Autogel in the treatment of patients with GEP-NETs. In 75 patients with symptoms of metastatic GEP-NETs who received dose-titrated lanreotide Autogel for 6 months, 65% and 18% of patients with flushing or diarrhea, respectively, at baseline achieved a $\geq 50\%$ reduction in frequency of symptoms⁵⁶.

Although octreotide quickly and effectively ameliorates symptoms in patients with carcinoid syndrome, the duration of effective treatment varies widely because of the development of escape from response^{57–64}. This loss of response to octreotide LAR in patients with GEP-NETs is in contrast to the durable response seen in patients with GH-secreting pituitary adenomas. The mechanisms underlying this phenomenon in patients with GEP-NETs remain unclear. However, it has been suggested that the loss of sensitivity may be due to either the outgrowth of *sst*₂-deficient tumor cell clones or a downregulation of *sst*₂ after prolonged exposure to agonists^{62,65}.

Safety and tolerability of octreotide

Octreotide has a well-established safety profile based on over 20 years of clinical experience. Both formulations are well-tolerated in most patients. Treatment discontinuations due to adverse events are rare.

The most frequent adverse events in patients receiving octreotide include pain at the injection site (10–20% of patients) and mild-to-moderate GI disturbances, such as loose stools, abdominal cramping, nausea and flatulence, which persist during therapy in only 5–15% of patients^{15,23,28,29,66–68}. Continuing treatment will often lead to a resolution of GI complications^{15,25,29}. No significant changes in routine biochemical and hematological variables have been reported. However, treatment with octreotide has the potential to alter glucose metabolism and patients with acromegaly and comorbid diabetes mellitus should be monitored carefully¹⁵.

Octreotide therapy also poses a risk of cholelithiasis, which may increase with longer treatment periods. Octreotide-associated biliary tract alterations, such as gallstones, sediment and sludge, have been variably reported in up to 20% of patients during octreotide treatment, but are usually asymptomatic and do not require surgical or medical therapy⁶⁹. The mechanism involved in the development of gallstones during therapy with somatostatin analogues is complex, although the main cause is thought to be the inhibition of cholecystokinin release from the small intestine, which results in reduced gallbladder emptying⁷⁰. Other mechanisms contributing to possible gallstone formation during somatostatin analogue therapy are increases in deoxycholic acid conjugates and cholesterol saturation, and inhibition of the usual prandial relaxation of the sphincter of Oddi⁷¹. It has been suggested

recently that patients who develop asymptomatic gallstones during therapy with somatostatin analogues are at high risk of developing symptoms if that therapy is discontinued⁷¹.

The next 20 years

Octreotide LAR is currently the leading medical therapy in acromegaly and GEP-NETs and will continue to be the mainstay for tumor control in these indications for the foreseeable future. It is effective in the majority of patients in controlling the biochemical and physiological symptoms of acromegaly and GEP-NETs, has proven antiproliferative effects in GH-secreting pituitary adenomas and metastatic functioning or nonfunctioning midgut NETs, and is well-tolerated, with an established safety profile. In addition, the less frequent administration regimen of octreotide LAR compared with subcutaneous octreotide offers benefits in terms of patient satisfaction and compliance. Due to its multiple mechanisms of action, clinical evaluation of octreotide is ongoing in a range of therapy areas, including oncology, gastroenterology and obesity.

Oncology

Antineoplastic effects observed in patients with acromegaly and GEP-NETs make octreotide an attractive candidate for the treatment of refractory solid tumors. Preclinical studies indicate that somatostatin analogues exert inhibitory and suppressive effects in prostate, gastric, lung, colorectal, mammary, thyroid, and pancreatic cell lines^{72,73}. When octreotide binds to tumors expressing somatostatin receptors, direct effects such as inhibition of the cell cycle and growth factors, and apoptosis occur⁷⁴. In addition, indirect antiproliferative effects include inhibition of growth factor and hormone release and angiogenesis, with modulation of the immune system⁷⁴. A range of clinical evaluations have shown mixed outcomes, but the therapeutic potential warrants further evaluation, possibly in combination with hormonal or cytotoxic therapies and in both adjuvant and neoadjuvant settings^{74,75}.

Advanced hepatocellular carcinoma is difficult to treat and survival is poor. In a pilot, 2-year study, octreotide LAR was evaluated in 30 patients; although the effect on survival appeared to be limited, 29% of patients did exhibit stable disease⁷⁶. Moreover, in a study by Dimitroulopoulos *et al.* (2007), survival was significantly improved in 31 patients who received octreotide for advanced hepatocellular carcinoma compared with placebo (49 vs. 28 weeks; $p < 0.01$)⁷⁷.

Treatment with radio-labeled octreotide in patients with inoperable or metastasized sst₂-positive tumors, including GEP-NETs, appears to be a promising new

therapy^{78,79}. In a phase I study, therapeutic effects, including one partial remission, six minor remissions, and stable disease in 14 tumors, were seen in 21/40 evaluable patients treated with multiple doses of radio-labeled octreotide, with only mild bone marrow toxicity. In three other phase I trials, 20% of patients experienced a partial response and 60% had stable disease⁷⁹.

Managing patients with severe GI symptoms

Octreotide may have a therapeutic effect in the management of diarrhea in patients receiving chemotherapy for cancer. In an open-label, randomized, multicenter study designed to assess the effects of two dose levels of octreotide LAR, 147 patients with active or prior chemotherapy-induced diarrhea and scheduled for chemotherapy were randomized to receive up to six doses of either octreotide LAR 30 or 40 mg. Both dose levels provided clinical benefit, although fewer patients in the 40-mg group than the 30-mg group experienced severe diarrhea, required intravenous fluid, and had diarrhea-related unscheduled healthcare visits⁸⁰. Another study has shown complete resolution of diarrhea in 30 of the 32 patients treated with octreotide⁸¹. Patients who suffer diarrhea as a complication of AIDS, graft-versus-host disease and tumor-related diarrhea can also obtain major benefit from treatment with octreotide⁸².

Symptoms associated with small intestinal involvement in patients with systemic sclerosis (SSc) are usually severe and resistant to treatment. To assess the safety and efficacy of octreotide in refractory small intestinal disease complicating SSc, seven patients with SSc non-responsive to traditional therapies received octreotide⁸³. All patients responded to octreotide, and a significant reduction in symptom severity was noted in the first month. A significant disturbance of defecation in two patients improved dramatically⁸³. These results suggest that long-term treatment with octreotide may be a safe and effective approach in the treatment of small intestinal disease in patients with SSc⁸³.

Obesity and polycystic ovary syndrome

Because octreotide reduces circulating levels of GH and insulin, it is a potential candidate for the treatment of obesity and polycystic ovary syndrome (PCOS), both of which include patients exhibiting insulin hypersecretion^{84,85}. A single-blind, placebo-controlled study in anovulatory abdominally obese women with PCOS has shown significant clinical benefits in patients who received octreotide⁸⁴. Octreotide produced significant decreases in fasting and glucose-stimulated insulin levels, increases in IGF-binding proteins, and improvements in hirsutism. Moreover, a trend toward greater reductions

in testosterone and androstenedione were observed in women treated with octreotide compared with those given placebo. All women treated with octreotide ovulated at the end of the study compared with only one of those receiving placebo ($p < 0.001$). Based on these results, the authors concluded that octreotide may be useful in hypocalorically dieting, abdominally obese PCOS women to improve hyperandrogenism and the insulin-IGF-I system.

Another randomized, double-blind, placebo-controlled trial has investigated the potential of octreotide LAR to improve weight loss, body mass index, and fasting serum insulin hypersecretion⁸⁵. After 6 months of treatment, patients receiving octreotide LAR 40 or 60 mg experienced statistically significant weight loss. However, the mean weight loss was modest (approximately 2 kg). A total of 7–21% of the patients taking octreotide LAR achieved a >5% decrease in body weight from baseline, compared with 11% in the placebo group. A *post hoc* analysis stratifying patients by race indicated that Caucasian patients with the greater degree of insulin hypersecretion appeared to derive the most benefit from treatment.

Conclusions

Over the past 20 years, octreotide has proven to be essential to the successful management of patients with acromegaly and GEP-NETs. The multiple effects of octreotide throughout the body, combined with its established safety profile, make it an appealing and reliable option for clinicians. The development of octreotide LAR offered a further advancement; less frequent dosing provided valuable benefits in quality of life to patients, with equivalent efficacy and tolerability. Moreover, recent results from the PROMID study have confirmed the antiproliferative effect of octreotide LAR in patients with well-differentiated metastatic GEP-NETs of the midgut. Exciting and new therapeutic uses of octreotide are currently under investigation in a variety of clinical settings.

Transparency

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Declaration of financial/other relationships

L.A. has disclosed that he has received grants from Imclone, Pfizer, Novartis and several other pharmaceutical companies, and that he has served as consultant for Pfizer, Novartis, Molecular Insights and Roche. He is also on speakers' bureaus for Amgen, Novartis, Bristol Myers, and several other pharmaceutical companies. P.U.F. has disclosed that Columbia

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