Role of Somatostatin Analogues in the Treatment of Neuroendocrine Tumors

Sujata Narayanan, MD, MS, and Pamela L. Kunz, MD

Abstract
Neuroendocrine tumors (NETs) are rare epithelial neoplasms with neuroendocrine differentiation that most commonly originate in the lungs and gastrointestinal tract. Many patients have advanced disease not amenable to surgery or local management. Some tumors also secrete amines, such as serotonin, that lead to syndromes of hormone excess, such as diarrhea and flushing. Thus, management of patients with NETs often requires a dual approach, including hormone symptom management and systemic tumor control. Somatostatin analogues have long been a mainstay of managing the hormone-related symptoms, and increasing evidence also supports their use for tumor control in patients with well-differentiated NETs. This article reviews the role of somatostatin analogues in the treatment of NETs. (J Natl Compr Canc Netw 2015;13:109–117)

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**Somatostatin Receptors**

Physiology of Somatostatin and Somatostatin Receptors

The somatostatin neuropeptide family includes 2 bioactive proteins: the predominant but functionally less active SST14, and a larger more potent molecular form, SST28.⁶ The somatostatins have a very short circulation half-life (≈2 minutes),⁷ and thus the somatostatin-producing cells are located close to its target cells.⁸ Both SST14 and SST28 act in an autocrine, paracrine, or neuronal regulatory manner, inhibiting glandular secretion, neurotransmission, smooth-muscle contractility, and absorption of nutrients. Somatostatin mediates its primarily inhibitory effects by binding to at least 5 high-affinity G-protein–coupled membrane receptors (SSTR1–5).⁹ The somatostatin receptors share approximately 40% to 60% homology, but mediate different biological actions on activation.¹⁰ All 5 somatostatin receptors have been identified throughout the central nervous system and gastrointestinal tract, in the endocrine and exocrine glands, and on inflammatory and immune cells. Tumors arising from somatostatin-target tissues, such as the pancreas and small intestine, express a high density of somatostatin receptors,¹¹–¹³ SSTR2 predominance is seen in most pancreatic and gastrointestinal-tract NETs.

The physiologic effects of somatostatin are largely inhibitory; it reduces gastrointestinal motility and gallbladder contraction; inhibits secretion of most gastrointestinal hormones, insulin, glucagon, and gastrin; reduces blood flow in the gastrointestinal tract; and inhibits growth hormone release from the pituitary gland and neurotransmission in the brain.¹⁴,¹⁵ Given this inhibitory profile of somatostatin, its activity has been used clinically for various indications, including the treatment of acromegaly, secretory diarrhea, and gastrointestinal bleeding; inhibition of tumor growth; treatment for symptoms of NET hormone excess; and imaging of neuroendocrine and other solid tumors.

Somatostatin was first used to control symptoms caused by NETs in the 1970s.¹⁶,¹⁷ However, given its molecular form, SST28.

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Somatostatin was first used to control symptoms caused by NETs in the 1970s. However, given its
short half-life requiring a cumbersome continuous infusion and rebound hypersecretion of hormones, its routine clinical application was limited. These properties of somatostatin resulted in the development of synthetic analogues beginning in the early 1980s, including octreotide and lanreotide, and, more recently, pasireotide. These peptides are more resistant to degradation, and their half-lives, and hence their biological activities, are substantially longer than those of native somatostatin (1.5–2 hours vs 1–2 minutes). They vary in their affinity toward different somatostatin receptor subtypes,10,19 and bind mainly to SSTR2, and much less to SSTR5. The newly developed somatostatin analogue pasireotide is a new “universal” or “pan-receptor” somatostatin analogue, having a high affinity for SSTR1, SSTR2, SSTR3, and SSTR5 subtypes.20 Table 1 lists the affinity of somatostatin and synthetic somatostatin analogues to the somatostatin receptor subtypes.20–22

### Somatostatin Analogues for Control of Hormone Release

#### Treating Symptoms of Hormone Excess

Octreotide was the first somatostatin analogue developed for clinical application, with 3 times more potency than naturally occurring somatostatin and a more practical half-life of 2 hours; it shows a high affinity toward SSTR2 and SSTR5. The short-acting formulation of octreotide can be given via continuous infusion or as a subcutaneous injection 2 to 3 times per day; it is not associated with the side effects of rebound hormonal hypersecretion. Longer-acting formulations were developed to provide more sustained drug levels, of which octreotide long-acting release (LAR) was the first in the 1990s. Octreotide LAR is administered at 20 to 30 mg as a monthly intramuscular injection. Continuing initial short-acting formulation coverage for approximately 2 to 3 weeks is generally recommended until steady-state levels of octreotide LAR are achieved. Studies comparing the shorter-acting and longer-acting forms of octreotide have demonstrated equal efficacy in terms of symptom control, with symptomatic response rates of 60% to 72% across groups.23

Lanreotide is another somatostatin analogue with similar somatostatin receptor–binding affinity as octreotide. Lanreotide has 2 formulations currently available: sustained-release lanreotide, given as an intramuscular injection every 2 weeks, and prolonged-release lanreotide, given as deep subcutaneous injections every 4 weeks. Lanreotide is approved both in Europe and the United States for treatment of acromegaly. Lanreotide has demonstrated symptom improvement in patients with carcinoid syndrome in several small prospective and retrospective studies.24–26 Short-acting octreotide and sustained-release lanreotide were shown to be equally effective in controlling carcinoid syndrome.27

### Table 1 Affinity of Somatostatin, Synthetic Somatostatin Analogues, and Radiopeptides to Somatostatin Receptor Subtypes

<table>
<thead>
<tr>
<th>Affinity to Somatostatin Receptors, IC50 (nmol)</th>
<th>SSTR1</th>
<th>SSTR2</th>
<th>SSTR3</th>
<th>SSTR4</th>
<th>SSTR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native somatostatin</td>
<td>SST28</td>
<td>5.2</td>
<td>2.7</td>
<td>7.7</td>
<td>5.6</td>
</tr>
<tr>
<td>Synthetic somatostatin analogues</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreotide</td>
<td>&gt;10,000</td>
<td>2.0</td>
<td>187</td>
<td>&gt;1,000</td>
<td>22</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>180</td>
<td>0.54</td>
<td>14</td>
<td>230</td>
<td>17</td>
</tr>
<tr>
<td>Pasireotide</td>
<td>9.3</td>
<td>1</td>
<td>1.5</td>
<td>&gt;100</td>
<td>0.16</td>
</tr>
<tr>
<td>Radiopeptides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[90Y-DOTA]-octreotide ([90Y-DOTATOC])</td>
<td>&gt;10,000</td>
<td>11</td>
<td>389</td>
<td>&gt;10,000</td>
<td>114</td>
</tr>
<tr>
<td>90Y-DOTA-lanreotide (DOTALAN)</td>
<td>&gt;10,000</td>
<td>23</td>
<td>290</td>
<td>&gt;10,000</td>
<td>16</td>
</tr>
<tr>
<td>[90Y-DOTA]-octreotate (DOTATE)</td>
<td>&gt;10,000</td>
<td>1.6</td>
<td>&gt;1000</td>
<td>523</td>
<td>187</td>
</tr>
<tr>
<td>[90Y-DOTA]-1-Nal-octreotide (DOTA-NOC)</td>
<td>&gt;1000</td>
<td>3.3</td>
<td>26</td>
<td>&gt;1000</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: IC50, Inhibitory concentration (half maximal); Y, yttrium.
Data from references 20–22.
a recent phase III study of lanreotide versus placebo in patients who were somatostatin analogue–naïve or responsive to conventional doses of octreotide, lanreotide reduced the need for short-acting octreotide (49% vs 34%; absolute difference 15%; P = .02); however, the results did not meet the predefined absolute difference of 30%.^28^ Pasireotide was developed as an agent with a broader somatostatin receptor profile similar to that of natural somatostatin. It binds with high affinity to somatostatin receptor subtypes SSTR1, SSTR2, SSTR3, and SSTR5 and displays a 30- to 40-fold higher affinity for SSTR1 and SSTR5 than octreotide or lanreotide.^20^ Given its greater binding affinity, hypotheses have proposed that it may have a greater inhibitory effect than octreotide on hormones secreted by carcinoid tumors.^29^ A multicenter, randomized, blinded phase III study of pasireotide LAR versus octreotide LAR in patients with symptomatic metastatic NETs showed that these drugs had equal efficacy in controlling symptoms of hormone secretion. The safety profile was similar, except regarding hyperglycemia, which was higher in the pasireotide arm (11% vs 0%).

Lastly, it has historically been recommended that patients with functional NETs receive prophylactic perioperative intravenous octreotide to prevent carcinoid crisis. Carcinoid crisis is thought to be a syndrome of sudden-onset severe carcinoid syndrome and vasomotor collapse. However, the physiology is poorly understood, and it is unclear which patients with NET are at risk for carcinoid crisis, and may include those with classic carcinoid syndrome and those with nonfunctional tumors.

Massimino et al^31^ recently reported a single-institution retrospective experience of 97 patients with carcinoid tumors undergoing surgery. This study found that octreotide LAR and bolus octreotide are insufficient in preventing intraoperative complications. Future definitive studies are needed to better understand carcinoid crisis and develop preventive strategies.

Dosing for Hormone-Related Symptoms
When somatostatin analogues are used for symptom control, the recommendation is to start short-acting somatostatin analogues immediately in an effort to provide immediate symptom relief, and then overlap them with long-acting somatostatin analogues until steady-state levels are reached (~2 weeks).^32^ The suggested starting dose of octreotide acetate ranges from 100 to 600 mcg/d in 2 to 4 divided doses; test doses are not routinely required. Doses are usually initiated at the lower dose range and can be individually titrated to control symptoms; some patients may require significantly higher doses (up to 1.5 mg/d).

The recommended dose of octreotide LAR is 20 to 30 mg via deep intramuscular injection repeated every 4 weeks. Correct intramuscular injection can be challenging. One report noted that only 52% of injections were successfully delivered and that correct intramuscular injection was associated with improved control of flushing among patients with carcinoid syndrome. Some patients also require “rescue” doses of short-acting octreotide to control breakthrough symptoms even after initiation of the long-acting formulation; these commonly occur in the days preceding a scheduled octreotide injection. Dose and frequency of both short- and long-acting somatostatin analogues may be further increased for symptom control as needed.^34^ Two controversial topics in somatostatin analogue dosing include the role of plasma octreotide levels and the risk of tachyphylaxis. Data showing a benefit associated with plasma octreotide monitoring are lacking, and therefore routine use is not recommended. Additionally, risk of tachyphylaxis after long-term use of somatostatin analogues has been postulated, although the mechanism of tachyphylaxis is poorly understood and rigorous prospective data are lacking.

Lastly, the dosing of somatostatin analogues in elderly patients with carcinoid syndrome requires special mention. Most patients with NETs are diagnosed in their seventh decade, with a median age of 63 years. In a recent study of the SEER-Medicare databases, Shen et al^35^ showed that only 50% of elderly patients with FDA-approved indications (carcinoid syndrome or metastatic disease) started octreotide LAR within 6 months of diagnosis, and that octreotide LAR use was lowest among patients aged 80 years and older. However, they also showed that the use of octreotide LAR within 6 months of diagnosis of carcinoid syndrome was associated with better survival for patients with metastatic disease. This study suggests that somatostatin analogue use in elderly patients with functional NETs may be underused and should be addressed in future studies.
Somatostatin Analogues for Control of Tumor Growth

Treatment for Control of Tumor Growth

Somatostatin analogues have also demonstrated antiproliferative properties in NETs, with varying effects depending on the primary site and somatostatin receptor subtype. For example, SSTR2 and SSTR5 have been shown to mediate the mitotic activity, leading to cell cycle arrest. Somatostatin analogues may also exert an indirect antiproliferative effect by inhibiting the release of growth factors and various trophic hormones, such as growth hormone, insulin-like growth factor-1, insulin, gastrin, and epidermal growth factor, both from the neoplastic cell and from the surrounding tumour matrix. Somatostatin analogues have also been postulated to reduce the vascularization of the neoplastic tissue in experimental models via inhibition of vascular endothelial growth factor.

The first clinical trial to demonstrate prolonged time to tumor progression (TTP) with somatostatin analogues in NETs was the PROMID study. In this phase III randomized, double-blind, placebo-controlled, multi-institutional German study, 85 patients with well-differentiated metastatic midgut NETs were randomized to receive 30 mg of octreotide LAR monthly via intramuscular injection versus placebo. Octreotide significantly improved TTP compared with placebo (14.3 vs 6.0 months in the placebo arm; hazard ratio [HR]=0.34; 95% CI, 0.20–0.59; P=.000072); median overall survival (OS) could not be calculated at the time of initial analysis. The study also found that functionally active and inactive tumors responded similarly, and the most favorable effect was observed in patients with low hepatic tumor volume and resected primary tumors. Updated OS data were presented in 2013; median OS was not reached in the octreotide LAR arm compared with 84 months in the placebo arm (HR, 0.85; CI, 0.46–1.56; P=.59). A survival benefit was seen for patients receiving octreotide LAR with low hepatic tumor volume (<10% liver involvement) but not for patients with high hepatic tumor volume (>10%). Although this study did not formally impact the FDA label for octreotide LAR, octreotide was widely adopted for controlling tumor growth in patients with metastatic midgut NETs.

The CLARINET study was a phase III randomized, double-blind, placebo-controlled, multina-
a longer median time from diagnosis. CLARINET contributes new information to the field, because it demonstrates the activity of somatostatin analogues in non-midgut tumors with higher grade and higher hepatic tumor volume, and raises the question whether somatostatin analogues should be used in patients with stable disease. However, the 18-month median progression-free survival in the placebo arm is encouraging and may also argue that active surveillance in select patients is reasonable. The CLARINET study has not demonstrated an OS difference, which could be attributed to crossover, need for longer follow-up, and perhaps a more indolent disease, as evidenced by a longer time from diagnosis compared with PROMID. Other completed and ongoing clinical trials evaluating somatostatin analogues for control of tumor growth in NETs are summarized in Tables 3 and 4.

**Dosing for Control of Tumor Growth**

Octreotide LAR, 30 mg via intramuscular injection monthly, and lanreotide, 120 mg via a deep subcutaneous injection are standard somatostatin analogue doses used for tumor control based on the PROMID and CLARINET studies, respectively. In contrast to dosing for hormone control, a 2-week overlap with short-acting octreotide is not required. Few high-level data support the routine use of below- or above-standard doses of somatostatin analogues for tumor control.

**Somatostatin Analogue Side Effects**

The most commonly encountered side effects of somatostatin analogues include nausea, abdominal cramps, diarrhea, steatorrhea, flatulence, hyperglycemia, and cholelithiasis/biliary sludging. Most of these symptoms are dose-dependent and resolve within the first few weeks of treatment. Cholelithiasis and/or gallbladder sludge occurs secondary to the inhibition of gallbladder contraction and emptying, and can develop in approximately 50% of patients on somatostatin analogues. Although this side effect is also dose-dependent, only 1% of patients develop acute symptoms requiring cholecystectomy. It has been recommended that cholecystectomy be performed prophylactically in patients with NETs who are undergoing or considering somatostatin analogue therapy. Local discomfort may also be experienced for all methods of administration (subcutaneous, deep subcutaneous, intramuscular injection). In patients with insulinomas, somatostatin analogues should be used with caution because they have the potential to worsen hypoglycemia by suppressing glucagon secretion.

**Radiolabelled Somatostatin Anal Ogues in NET Therapeutics**

Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues is a relatively new and promising treatment modality for patients with inoperable or metastatic NETs. This treatment is based on the same principle used in somatostatin receptor scintigraphy, such as indium-111 ($^{111}$In)–labeled octreotide scintigraphy (OctreoScan) and the newer gallium-68 ($^{68}$Ga)–labeled DOTA PET scans. The radiolabeled somatostatin analogues

<table>
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<tr>
<th>Phase</th>
<th>Therapy</th>
<th>n</th>
<th>Patients</th>
<th>TTP or PFS (mo)</th>
<th>OS (mo)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-agent studies</strong></td>
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<td></td>
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<tr>
<td>II (PROMID)</td>
<td>Octreotide vs placebo</td>
<td>85</td>
<td>Midgut</td>
<td>14.3 vs 6.0</td>
<td>NR</td>
<td>2%</td>
</tr>
<tr>
<td>III (CLARINET)</td>
<td>Lanreotide vs placebo</td>
<td>204</td>
<td>Pancreas, midgut, hindgut, unknown</td>
<td>18.0 vs NR</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Combination studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>III (RADIANT-2)</td>
<td>Everolimus/octreotide vs placebo/octreotide</td>
<td>429</td>
<td>NETs with carcinoid syndrome</td>
<td>16.4 vs 11.3a</td>
<td>NR</td>
<td>2% vs 2%</td>
</tr>
<tr>
<td>III (SWOG 0518)</td>
<td>IFN/octreotide vs bevacizumab/octreotide</td>
<td>400</td>
<td>High-risk NETs</td>
<td>DSMC reported as negative study; formal data pending</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DSMC, data safety and monitoring committee; NA, not applicable; NR, not reached; OS, overall survival; PFS, progression-free survival; RR, relative risk; TTP, time to progression.

*Not statistically different.
Somatostatin Analogues in Treatment of NETs

bind to somatostatin receptors and are internalized into the tumor cells, where they can be used for diagnostic and therapeutic purposes (“theranostics”). Through targeting somatostatin receptors in NETs with radiolabeled somatostatin analogues, a tumoricidal radiation dose is delivered, thus causing a localized antitumor effect.⁴²

Somatostatin peptides with higher receptor affinity are conjugated with radiometal-labeling chelators. DOTA is a chelator capable of encapsulating hard metals, such as gallium, yttrium, or lutetium. The first generation of PRRTs in the 1990s used ¹¹¹In, a γ-emitter.⁴³,⁴⁴ Although these showed encouraging responses in terms of symptom relief, tumor shrinkage, and patient survival, they were also associated with significant bone marrow toxicity, including myelodysplastic syndrome and leukemia. The second generation of PRRTs used yttrium-90 (⁹⁰Y)–labeled DOTA³,Tyr³-octreotide, which has been evaluated in several phase I to II studies.⁴⁵–⁴⁹ ⁹⁰Y is a pure β-emitter with a relatively long tissue penetration range (12 mm), which enables it to easily penetrate larger lesions. These studies reported modest response rates, ranging from 25% to 30%. However, renal toxicity was noted to be a common dose-limiting side effect of this treatment, and the administration of ⁹⁰Y PRRT required amino acid infusion for nephroprotection. Since 2000 lutetium-177 (¹⁷⁷Lu)-labeled DOTA³,Tyr³-octreotide has been used for PRRT. ¹⁷⁷Lu is a medium-energy β-emitter with an approximate half-life of 6.7 days and a maximal tissue penetration of 2 mm. Table 1 lists the affinity of somatostatin and radiopeptides to the somatostatin receptor subtypes.

In 2008, Kwekkeboom et al⁵⁰ reported a retrospective analysis of 500 patients treated with [¹⁷⁷Lu-DOTA³,Tyr³]-octreotate up to a cumulative dose of 750 to 800 mCi (27.8–29.6 GBq), usually in 4 treatment cycles, with treatment intervals of 6 to 10 weeks. Complete and partial tumor remissions occurred in 2% and 28% of the patients, respectively, and minor tumor response (decrease in size >25% and <50%, respectively) occurred in 16%. Median time to progression was 40 months, and median OS from start of treatment was 46 months. Acute toxicities included nausea and vomiting, and subacute toxicities included grade 3/4 hematologic toxicity (in 9.5% of patients 4–8 weeks after 3.6% of administrations) and alopecia (62.0%). Nine patients experienced serious delayed toxicities, including renal insufficiency (n=2), liver toxicity (n=3), and myelodysplastic syndrome (n=4).

Although PRRT has been used for the treatment of metastatic somatostatin receptor–positive NETs in Europe since the 1990s, it is not approved by the FDA because of the lack of randomized data. The first phase III, randomized, multinational clinical trial of PRRT is now underway. The NETTER-1 study will compare ¹⁷⁷Lu-DOTA³,Tyr³-octreotate to high-dose octreotide LAR (60 mg monthly) in patients

### Table 4 Select Ongoing Randomized Clinical Trials With Somatostatin Analogues

<table>
<thead>
<tr>
<th>Phase</th>
<th>Therapy</th>
<th>n</th>
<th>Patients</th>
<th>Primary End Point</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>II (COOPERATE-2)</td>
<td>Everolimus vs everolimus/pasireotide</td>
<td>160</td>
<td>pNET</td>
<td>PFS</td>
<td>NCT01374451</td>
<td>Closed to accrual</td>
</tr>
<tr>
<td>III (NETTER-1)</td>
<td>[¹⁷⁷Lu-DOTA³,Tyr³]-octreotate vs high-dose octreotide</td>
<td>280</td>
<td>Midgut</td>
<td>PFS</td>
<td>NCT01578239</td>
<td>Enrolling</td>
</tr>
<tr>
<td>III (LUNA)</td>
<td>Pasireotide vs everolimus vs both</td>
<td>120</td>
<td>Lung/thymus</td>
<td>PFS (9-mo)</td>
<td>NCT01563354</td>
<td>Enrolling</td>
</tr>
<tr>
<td>III (CASTOR)</td>
<td>[¹⁷⁷Lu-DOTA⁰,Tyr³]-octreotate vs IFN</td>
<td>60</td>
<td>GI NET</td>
<td>PFS</td>
<td>NCT01860742</td>
<td>Belgium, opening 2015</td>
</tr>
<tr>
<td>II/III (REMINET)</td>
<td>Lanreotide vs placebo after SD/CR on chemotherapy or biotherapy</td>
<td>118</td>
<td>pNET</td>
<td>PFS (6-mo)</td>
<td>-</td>
<td>Europe, opening 2015</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; GI, gastrointestinal; IFN, interferon; NET, neuroendocrine tumor; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumor; SD, stable disease.
with inoperable, somatostatin receptor–positive metastatic midgut NETs who have experienced progressive disease on standard doses (20–30 mg every 3 to 4 weeks) of octreotide LAR (ClinicalTrials.gov identifier: NCT01578239). The accrual goal is 280 patients and the primary end point is progression-free survival. Additionally, novel radiolabelled somatostatin antagonists are being developed for both imaging and treatment.  

Future Directions

Considerable advances have been made in the treatment of NETs in the past decade. Although the use of somatostatin analogues for symptom control has been prevalent for decades, somatostatin analogues have recently been shown to also serve as antiproliferative agents. Given that somatostatin analogues have a favorable side effect profile, they are a reasonable option early in the disease course and may also serve as building blocks for combination therapies. Prospective clinical trials are also underway to evaluate radiolabeled somatostatin agonists and antagonists.

References

Somatostatin Analogues in Treatment of NETs


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Posttest Questions

1. Which of the following nonsurgical options may be used in the management of unresectable metastatic neuroendocrine tumors?
   a. Cytotoxic chemotherapy
   b. Somatostatin analogues
   c. Liver-directed therapies
   d. Systemic therapy with molecularly targeted agents
   e. All of the above
   f. None of the above

2. True or False: Hyperglycemia, diarrhea, and steatorrhea are possible side effects of somatostatin analogues.

3. The suggested starting dose of octreotide acetate ranges from:
   a. 100 to 200 mcg/d in 2 to 4 divided doses without a routine test dose
   b. 100 to 600 mcg/d in 2 to 4 divided doses without a routine test dose
   c. 100 to 600 mcg/d in 2 to 4 divided doses with a routine test dose
   d. 200 to 400 mcg/d in 2 divided doses