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Octreotide and Lanreotide in Gastroenteropancreatic Neuroendocrine Tumors

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Abstract Neuroendocrine tumors are heterogeneous, rare malignancies that arise most commonly in the gastrointestinal tract and pancreas. They often secrete vasoactive substances resulting in carcinoid syndrome and the tumor cells exclusively express somatostatin receptors. Octreotide and lanreotide are the two synthetic somatostatin analogs used for the control of carcinoid symptoms and tumor progression in advanced inoperable disease. Recent pivotal trials (PROMID and CLARINET studies) established their antitumor activity. We discuss the available data to support their use as symptom controlling and antiproliferative agents. This article also reviews the guidelines (National Comprehensive Cancer Network and North American Neuro Endocrine Tumor Society), cost-analysis (suggesting the cost-effectiveness of lanreotide autogel compared to higher doses of octreotide long acting release formulation in refractory patients), and future directions of somatostatin analogs in the management of patients refractory to conventional doses of octreotide and lanreotide.

Keywords Octreotide · Lanreotide · Synthetic · Somatostatin · Gastroenteropancreatic · Neuroendocrine tumors · Cost-analysis

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies that appear to be increasing in incidence in the USA, with an estimated incidence of 5.25 cases per 100,000 people in the year 2004, suggesting approximately fivefold increase between 1973 and 2004 [1]. Gastroenteropancreatic (GEP) NETs constitute approximately 55 % of those cases [1]. A more recent updated analysis of Surveillance, Epidemiology and End Results (SEER) registry (1973–2007) with approximately 29,000 patients with GEP NETs, showed an annual incidence of 3.65/100,000 individuals [2], suggesting a 3.6-fold increase in the age-adjusted incidence of GEP NETs over the last 4 decades [3]. GEP NETs have various clinical presentations depending on the site of origin and the secretion of hormones. Majority of GEP NETs arise in small intestine (30.8 %), while approximately 26, 18, and 12 % of them occur in rectum, colon, and pancreas, respectively [4]. Most of them (60–80 %) [5] present with metastatic disease. Metastatic midgut NETs often result in carcinoid syndrome by secreting serotonin and other vasoactive substances [6]. Pancreatic NETs can be silent (approximately 50 % of them) or secrete various peptide hormones like insulin, glucagon, and gastrin [4]. Somatostatin, originally described as an inhibitor of growth hormone release, was shown to inhibit gastrointestinal endocrine secretion in a paracrine fashion [7] and subsequently, synthetic somatostatin analogs (SSAs) with longer half-lives were developed to palliate the hormonal symptoms. Recently, SSAs like octreotide [8] and lanreotide [9••] were shown to control disease progression in well-differentiated, metastatic midgut NETs and well/moderately differentiated, metastatic nonfunctioning GEP-NETs

respectively. In this review, we discuss the evolving role of octreotide and lanreotide as symptom controlling and antiproliferative agents.

Carcinoid Symptom Control with Octreotide and Lanreotide

Octreotide acetate (Sandostatin; Novartis, East Hanover, NJ, USA) was the first SSA developed in 1980s. It had a shorter peptide length (of 8 aminoacids only), longer half-life (1.5 to 2 h [10]) and was more potent and resistant to degradation compared to the native somatostatin [11]. It binds with higher affinity to somatostatin receptor (SSTR) subtype 2 and 5 [12, 13]. Octreotide was studied in managing hormonal symptoms from neuroendocrine tumors. The starting dose ranged from 150 to 250 mcg given subcutaneously 3 to 4 times a day and can be titrated up to control symptoms [14]. This dose range produced prompt resolution of flushing, diarrhea, and a biochemical response (50 % or more decrease in urinary 5-hydroxyindoleacetic acid levels) in 72 % of the patients with a median duration of response for more than 12 months [14].

Octreotide long-acting release (LAR) depot formulation was developed in the early 1990s by Novartis, Basel, Switzerland. It had octreotide encapsulated in microspheres of a slowly dissolving polymer and thus provided a slow drug release after intramuscular (IM) administration. Astruc et al. [15] described the predictable steady-state pharmacokinetic profile of octreotide LAR 20 mg administered intramuscularly every 28 days. Octreotide LAR (10, 20, or 30 mg IM every 4 weeks) was compared to subcutaneous (SC) octreotide (every 8 h) in patients with malignant carcinoid syndrome by Rubin et al. [16]. The control of diarrhea was similar in all the four treatment groups but the group receiving 10 mg of octreotide LAR had the least effective control of flushing. Thus, octreotide LAR (starting dose of 20 mg) had equal efficacy compared to multiple SC injections of the short acting formulation and it was recommended for symptom control in neuroendocrine tumors.

Higher doses of octreotide LAR (>30 mg/month) are frequently used in clinical practice for refractory carcinoid symptoms and several studies have reported better symptom control at higher doses. Broder et al. [17••] performed a systematic literature review of all those studies (including both retrospective and prospective studies); however, a meta-analysis could not be performed due to the heterogeneity in their design, patient population, and octreotide LAR regimens (doses ranging from 40 mg every month or 30 mg every 3 weeks up to 120 mg every month were used in these studies). The benefit with octreotide LAR doses >60 mg/month was negligible [18]. None of these studies reported increased toxicity with >30 mg/month dose of octreotide LAR, suggesting that higher doses for refractory carcinoid syndrome are well tolerated.

Lanreotide (Somatuline; Ipsen, Paris, France) is another SSA octapeptide that was initially developed in 1990s, as a sustained release formulation, administered intramuscularly every 2 weeks, producing a 50 % reduction in symptoms and urinary 5-hydroxyindoleacetic acid levels in approximately 55 and 42 % of patients, respectively [19]. The affinity of lanreotide to SSTR 2 and 5 is similar to that of octreotide [20]. O'Toole et al. [21] compared octreotide (200 microg SC twice or thrice daily) with lanreotide (30 mg IM every 10 days) in a prospective crossover study of carcinoid syndrome patients and found them to be equally efficacious in controlling symptoms and reducing tumor markers.

Lanreotide was reformulated in 2003 by Ipsen biopharmaceuticals as a slow release deep SC depot preparation known as lanreotide autogel [22, 23], available as small volume prefilled syringes (eliminating the need for reconstitution) at doses 60, 90, or 120 mg given once a month. This formulation (at a dose of 120 mg) was compared to the sustained release microparticle formulation in patients with well-differentiated neuroendocrine tumors by Bajetta et al. [24] in a phase III trial, which showed that the SC lanreotide autogel was non-inferior to the IM preparation in controlling the tumor markers and stabilization of tumor size.

Several European studies confirmed the usefulness of lanreotide autogel in carcinoid symptom control. A multicenter, uncontrolled dose titration study of lanreotide autogel in carcinoid syndrome, showed a significant decrease (≥50 % reduction from baseline) of flushing in 65 % patients and diarrhea in 18 % patients, along with a median 24 % decrease in urinary 5-hydroxyindoleacetic acid levels. This study used 90 mg lanreotide autogel for the first two monthly doses and the subsequent doses were titrated (60 or 90 or 120 mg) depending on the symptom response. A 9-year retrospective study from Khan et al. [25] reported good symptom control in 74 % of neuroendocrine tumor patients receiving lanreotide autogel (60, 90, or 120 mg with dose titration as needed). It also showed stable clinical and radiographical disease in 54 % patients after a 33-month median follow-up. A very good patient-reported satisfaction in hormonal symptom control (76 % patients with diarrhea and 73 % patients with flushing) was also reported in GEP NET patients with carcinoid syndrome who received lanreotide autogel at a median dose of 120 mg [26]. Recently, phase III placebo controlled ELECT study showed that lanreotide autogel 120 mg lowered the use of rescue short acting octreotide for carcinoid symptoms by approximately 15% [34 % (lanreotide arm) versus 49 % (placebo arm); $p = 0.02$] [27].

In summary, both octreotide and lanreotide have similar mechanisms of action with similar SSTR binding affinities. Both of them have similar symptom control rates in carcinoid syndrome patients with approximately 60–72 % and 55–75 % of patients reporting symptomatic control while receiving octreotide [14, 16] and lanreotide [19, 25], respectively. The

starting dose of octreotide LAR for symptom control would be 20 mg (IM every 4 weeks) titrating up to 30 mg for better symptom control. However, doses >30 mg/month are widely used in clinical practice. Strosberg et al. [28] reported expert clinical opinion suggesting an increase in dose/frequency of octreotide LAR up to 60 mg/month or up to 40 mg every 3 weeks as second line therapy for uncontrolled secretory symptoms in neuroendocrine tumors. Three different doses of lanreotide autogel (60, 90, and 120 mg; deep SC every 4 weeks) were studied for symptom control with titration as needed. However, the use of doses >120 mg has not been investigated. There are currently no head to head comparisons of octreotide LAR and lanreotide autogel for symptom control in neuroendocrine tumor patients.

Antiproliferative Effects of Octreotide and Lanreotide

Several preclinical studies revealed the antiproliferative effects of SSAs in NETs. These effects are partly due to the SSTR mediated regulation of PI3K/Akt signaling (MAP kinase) pathway, resulting in increased tumor suppressor gene expression, induction of cell cycle arrest, and apoptosis [29]. Certain indirect mechanisms resulting in restricted proliferation including inhibition of secretion of growth factors and suppression of tumor angiogenesis are also described [30, 31].

Early non-placebo controlled clinical trials of octreotide and lanreotide in GEP NETs supported these antiproliferative mechanisms by tumor stabilization and some partial responses. Octreotide LAR (20 to 30 mg IM every 4 weeks) resulted in stable disease in 38–88 % of patients with advanced, metastatic, functioning, or nonfunctioning GEP NETs, while lanreotide autogel (60 or 120 mg deep SC every 4 weeks) produced 40–89 % tumor stabilization [32]. Recent placebo controlled PROMID (Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors) and CLARINET (Controlled Study of Lanreotide Antiproliferative Response in NeuroEndocrine Tumors) studies confirmed the antitumor activity of octreotide LAR and lanreotide autogel, respectively.

PROMID [8] was a double blind, phase III multi-institutional German study of 85 treatment-naïve patients with metastatic or locally inoperable, well-differentiated (grade 1) midgut neuroendocrine tumors, who were randomized to conventional dose of octreotide LAR 30 mg IM every 28 days or placebo. Approximately 39 % of patients in PROMID were symptomatic/had carcinoid syndrome. The primary efficacy endpoint, time to tumor progression (TTP) was significantly better in the treatment group (14.3 versus 6 months in placebo, hazard ratio [HR] = 0.34; 95 % CI, 0.20 to 0.59; $p = 0.000072$), confirming the antiproliferative response. This was irrespective of the tumor functionality. The response was greatest in those with resected primary tumor and those with low (≤10 %) liver tumor burden. Arnold et al. [33] provided updated results on median overall survival which was not reached for octreotide arm versus 84 months in placebo; this was not significantly different between the two arms (HR = 0.85; 95 % CI, 0.46 to 1.56; $p = 0.59$). Thus, PROMID study established octreotide LAR as an antitumor agent in patients with metastatic or inoperable, functional or nonfunctional, well-differentiated midgut neuroendocrine tumors with resected primary and low hepatic tumor burden.

CLARINET [9••] was another multinational, randomized, double-blind, placebo-controlled phase III study of 204 patients with nonfunctioning, metastatic or locally inoperable, well- or moderately-differentiated (grade 1 and 2) GEP NETs, who were randomized to lanreotide autogel (120 mg, deep SC, every 28 days; maximum of 24 injections) or placebo. The primary efficacy endpoint, progression-free survival, was significantly better in the treatment group (not reached versus 18 months in placebo, HR for progression or death = 0.47; 95 % CI, 0.30 to 0.73; $p < 0.001$). The 2-year progression-free survival was better in the treatment arm (65.1 %) versus placebo (33 %). Overall survival was not significantly different between the two arms at 2 years, attributable to the cross-over from placebo to active treatment upon disease progression. The treatment arm had favorable HRs for disease progression or death among the different subgroups of patients with pancreatic, midgut, grade 1 and 2 NETs (greatest benefit was in midgut NETS with a HR of 0.35), except for the smaller subgroup of hindgut NETs. In addition, the CLARINET study included patients with larger hepatic tumor burden (≤25 or >25 %) and irrespective of the liver tumor volume, the lanreotide arm demonstrated a better progression-free survival than placebo. Thus, CLARINET study established the antitumor activity of lanreotide autogel in metastatic or inoperable, nonfunctioning, well- or moderately-differentiated GEP NETs regardless of hepatic tumor burden.

Table 1 depicts the major differences between the two trials. CLARINET included patients with higher grade (G2), larger hepatic tumor burden, and patients with non-midgut NETs (pancreatic and hindgut). Most of the patients in the CLARINET study (96 %) had no tumor progression 3–6 months prior to randomization, suggesting a very indolent disease population; while this data was not available in the PROMID study, all patients were within 6–8 months of diagnosis. Placebo groups had very different progression-free survival in both trials which

Table 1 Differences between PROMID and CLARINET trials. Neuroendocrine tumor (NET), metastases (mets), grade 1 (G1), grade 2 (G2), time to tumor progression (TTP), progression-free survival (PFS), hazard ratio (HR)

	PROMID ($n = 85$)	CLARINET ($n = 204$)
Primary NET location	Midgut (75 %) or unknown (25 %)	Pancreas (44 %), midgut (36 %), hindgut (7 %), or unknown (13 %)
Liver metastasis and the hepatic tumor burden	73 patients (86 %) had liver mets; of them, 71 % had <10 % and 29 % had >10 % hepatic tumor burden	All patients (100 %) had liver mets; of them, 67 % had ≤25 % and 33 % had >25 % hepatic tumor burden
Tumor grade and Ki67	Well differentiated (G1) Ki-67 ≤2 %	Well (G1) or moderately (G2) differentiated Ki-67 ≤2 % in 69 %, Ki-67 3–10 % in 31 % of the cohort
Tumor functionality	39 % patients had mild symptoms (flushing that was tolerable without intervention and diarrhea that responded to treatment with loperamide or cholestyramine)	Nonfunctioning in all patients
Octreoscan positivity required for enrollment	No	Yes
Tumor progression in 3–6 months before randomization	Undocumented	Absent in 96 % of patients
Response criteria	Bidimensional WHO criteria	Unidimensional RECIST version 1.0 criteria
Treatment-naïve	All patients	Only 84 % were treatment naive
Median time since diagnosis	Octreotide - 7.5 mts, placebo - 3.3 mts	Lanreotide - 13.2 mts, placebo - 16.5 mts
Primary tumor resection	56 patients (66 %)	79 patients (39 %)
TTP/PFS	TTP: 14.3 mts (octreotide) versus 6 mts (placebo), HR = 0.34; 95 % CI, 0.20 to 0.59	PFS: not reached (lanreotide) versus 18 mts (placebo), HR = 0.47; 95 % CI, 0.30 to 0.73. HR for midgut subgroup = 0.35; 95 % CI, 0.16 to 0.80

may be explained by the response criteria used in the two trials. The two-dimensional WHO response criteria (used in PROMID) would show a greater percentage increase in the tumor size than unidimensional RECIST criteria (used in CLARINET) for the same tumor response, thus showing a shorter progression-free survival. These above factors might explain the longer progression-free survival seen in CLARINET compared to PROMID in the treatment arms. Both octreotide and lanreotide were well tolerable with similar mild side effect profiles including nausea, steatorrhea, bloating, and risk of gall stones/sludge with long-term administration. The doses selected for these trials were 30 mg of octreotide LAR and 120 mg of lanreotide autogel.

Guidelines for SSA Use

FDA (Food and Drug Administration) Octreotide has been used in USA for carcinoid symptom control and it was originally approved by FDA in 1987 for functioning NETs. The short acting form, which required 3 to 4 times daily dosing, was replaced by the LAR formulation in 1990s and the FDA label suggested a starting dose of 20 mg octreotide LAR (with titration to 30 mg for symptom control) after Rubin et al. [16] published their study results comparing LAR formulation with the short acting SC form; the approval to date remains for control of carcinoid symptoms despite the additional data on antitumor activity.

Lanreotide on the other hand has been approved for acromegaly many years ago but was only recently approved by FDA in December' 2014, for antitumor activity in metastatic GEP NETs and is the first SSA approved in this setting. It is approved for symptom control in more than 50 countries but not yet for this indication in the USA.

NANETS (North American Neuro Endocrine Tumor Society) Consensus Guidelines 2013 The NANETS committee includes two categories of recommendations as either 'Consider' (weaker evidence) or 'Recommend' (stronger evidence) and these are outlined in Table 2 [34••].

NCCN (National Comprehensive Cancer Network) Current NCCN guidelines [35••] recommend short acting octreotide (150 to 250 mcg SC three times daily) or octreotide LAR (20 to 30 mg IM every 4 weeks) for symptom control in neuroendocrine tumors, with a suggestion to increase dose/frequency as needed. Octreotide LAR (20–30 mg IM monthly) and lanreotide autogel (120 mg deep SC monthly) are also recommended for control of tumor growth in metastatic GEP NETs with significant tumor burden. These recommendations are based upon lower-level evidence and there is uniform NCCN consensus that these interventions are appropriate (category 2A recommendation).

Progressing NETs The dose of octreotide LAR currently recommended for tumor control in GEP NETs is 20–30 mg IM monthly, although the dose used in PROMID study producing

Table 2 NANETS 2013 consensus guidelines [34••]. Long acting release (LAR), neuroendocrine tumor (NET), intra-muscular (IM)

		Recommend	Consider
Octreotide LAR 20–30 mg IM for carcinoid symptom control	Gastrointestinal NETs	✓	–
	Pancreatic NETs	✓	–
Octreotide LAR doses could be escalated or interval shortened for refractory symptoms	Gastrointestinal NETs	✓	–
	Pancreatic NETs	–	✓
Octreotide LAR for tumor control in newly diagnosed metastatic disease with low/intermediate/high tumor volume	Gastrointestinal NETs	–	✓
	Pancreatic NETs	–	–
Octreotide LAR for tumor control in progressive disease	Gastrointestinal NETs	–	✓
	Pancreatic NETs	–	✓

antiproliferative effect was 30 mg (not 20 mg). Also, midgut NETs only were included in PROMID and no randomized studies to date have shown antitumor effect of octreotide in pancreatic NETs. As both octreotide and lanreotide have high affinity for SSTR-2 and more than 80 % of GEP NETs have predominant expression of SSTR-2 [36, 37], the NCCN panel believes that either of them is appropriate for tumor control in GEP NETs.

Cost Analysis

The cost difference between the two agents at doses used in the pivotal trials (30 mg octreotide LAR compared to 120 mg lanreotide autogel) is approximately $1045 (Lantreotide being the more expensive formulation). Given the long term use of these agents in this disease, use of octreotide 30 mg for tumor control in a GEP NET patient would cost approximately $12,500 per year less compared to lanreotide autogel. These values are based on acquisition costs for a high volume pharmacy (refer Tables 3 and 4).

However, some studies showed better antitumor activity with >30 mg/month doses of octreotide LAR. Chadha et al. [38] showed retrospectively that high doses of octreotide LAR [median of 40 mg (range was 40 to 90 mg)] in GEP NET patients prolonged the time for further treatment interventions compared to conventional dose (17.7 months for high dose group versus 2.9 months for conventional dose group; $p = 0.12$). Another retrospective study by Anthony et al. [39] showed stable disease in 55 and 50 % patients with NETs receiving 40 and 60 mg/month of octreotide LAR, respectively. A small study by Ferolla et al. [40] evaluated 30 mg octreotide LAR given every 3 weeks in well-differentiated NET patients with progressive disease on standard-dose interval and showed a longer progression-free survival of 30 months. These suggest that higher doses can provide greater antitumor benefit for some patients, although this is not confirmed in large randomized prospective trials.

Nonetheless, there are no randomized studies that compared higher doses of octreotide LAR with 120 mg lanreotide autogel after progression on conventional LAR formulation. Furthermore, even though lanreotide formulations available are 60, 90, and 120 mg, all studies of antitumor effect have evaluated 120 mg dose and no data on further dose escalation are yet available. However, more frequent administration of lanreotide every 3 or even every 2 weeks has been suggested for symptom management and there have been several pharmacokinetic studies in overweight individuals suggesting a lower drug exposure in those with a higher body mass index [41–43]. In most of the lanreotide studies, few patients (16 % [25] and 56 % [27]) were on conventional dose octreotide LAR (≤30 mg) prior to initiation of lanreotide, supporting the feasibility of sequential use.

If 120 mg of lanreotide autogel is used (as opposed to the use of higher doses of octreotide LAR) for poor symptom control or disease progression on conventional dose octreotide LAR in GEP NET patients, there would be cost savings, as higher doses of octreotide LAR (40 mg and 60 mg) are more expensive than 120 mg lanreotide autogel. Approximately $5000 and $39,800 would be saved annually for each patient

Table 3 Cost per successful injection. Long acting release (LAR)

Lanreotide autogel (120 mg)	Octreotide LAR (30 mg)	Octreotide LAR (40 mg)	Octreotide LAR (60 mg)
$5407	$4361.54	$5825.38	$8723.08

Table 4 Cost savings with synthetic somatostatin analogs. Long acting release (LAR)

	Per successful injection (1 dose)	Per patient per year (12 doses)
Cost savings with octreotide LAR 30 mg (compared to lanreotide autogel 120 mg)	$1045.46	$12,545.52
Cost savings with lanreotide autogel, 120 mg (compared to 40 mg octreotide LAR)	$418.38	$5020.56
Cost savings with lanreotide autogel, 120 mg (compared to 60 mg octreotide LAR)	$3316.08	$39,792.96

receiving 40 and 60 mg/month of octreotide LAR, respectively, if they were switched to 120 mg lanreotide autogel (refer Table 3 and 4). Currently, at our center (Roswell Park Cancer Institute), 78 % of NET patients are on 30 mg/month of octreotide LAR compared to 22 % on higher doses (18 % on 40 mg and 4 % on 60 mg) for either disease progression or refractory carcinoid symptoms. Usage of lanreotide autogel 120 mg in these 22 % patient population on a long-term basis would save approximately $10,400 per year, compared to higher doses.

Differences in the Administration of Octreotide LAR and Lanreotide Autogel

Octreotide LAR requires reconstitution before injection which must be carried out by a trained health-care professional. In contrast, lanreotide autogel comes in low volume prefilled syringes eliminating the need for reconstitution and it can be administered with a greater confidence that a full dose would be delivered. Self or partner administration of lanreotide autogel at home (after proper injection technique training) was found to be safe and effective in acromegaly patients [44, 45], thus preventing monthly hospital visit and its associated cost. A study by Adelman et al. [46] evaluated the preference for these devices among nurses in Europe/USA and found that using lanreotide autogel was easy, time saving, and associated with low clogging risk compared to LAR formulation, which would also be appreciated by patients. Another European study [47] confirmed the substantial cost savings related to fewer clogging events and shorter administration time with lanreotide autogel compared to the regular octreotide LAR in acromegaly and NET patients.

Future of Somatostatin Analogs in the Management of Net Patients Refractory to Current Conventional Treatments

Pasireotide (SOM230) is a newer SSA with broader and higher affinity to SSTRs compared to octreotide and lanreotide [48]. The rapid acting SC form was shown (in a phase II trial) to be effective in controlling carcinoid symptoms of metastatic NET patients that were refractory to octreotide LAR [49]. Upfront pasireotide LAR (60 mg) in treatment-naïve patients with metastatic grade 1 or 2 GEP NETs was studied in a recent phase II trial, producing 60 % stable disease and a median progression-free survival of 12.2 months [50]; however, high incidence of hyperglycemia (14 % grade 3 hyperglycemia) requiring insulin administration questioned its suitability as a first-line agent. In a recent phase III study of metastatic NETs with progressive symptoms on the maximum approved dose of available SSA, patients were randomized to pasireotide LAR (60 mg) and octreotide LAR (40 mg), both given IM every 28 days [51]. This study was halted after an interim analysis showed no difference in symptom response rates, the primary end-point. However, pasireotide produced better tumor shrinkages than octreotide and investigator-assessed progression-free survival was better in pasireotide arm by 5 months (11.8 versus 6.8 months; HR = 0.46; $p = 0.045$), suggesting the higher antitumor efficacy of pasireotide. The safety profile of pasireotide was similar to octreotide, except for higher frequency of hyperglycemia (11 % with pasireotide versus 0 % with octreotide).

The new oral small-molecule inhibitor of tryptophan hydroxylase, Telotristat etiprate (LX1606), was shown to inhibit the peripheral synthesis of serotonin and decrease urinary 5-hydroxyindoleacetic acid levels in phase I studies of healthy volunteers [52]. Doses up to 500 mg TID orally were used in these studies. A small prospective randomized study evaluated sequential, escalating doses of telotristat in 23 patients with neuroendocrine tumorrelated diarrhea inadequately controlled on octreotide LAR [52]. Approximately 17 % of these patients were on conventional dose of octreotide LAR (30 mg/month), while the remaining (83 %) were on higher doses (30 mg/3 weeks or 40 mg/2–4weeks or 60 mg/3 weeks). This study showed a 28 % control in diarrhea (≥30 % reduction in stool frequency for ≥2 weeks) and a 56 % biochemical response (≥50 % reduction or normalization in 24-h urinary 5-hydroxyindoleacetic acid levels). Also, this oral drug was well tolerated with mild nausea, vomiting, and abdominal discomfort being the frequently reported adverse

events. Currently, a phase III, randomized, placebo-controlled TELESTAR (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome) study (NCT01677910) is ongoing, evaluating the efficacy and safety of Telotristat (250 mg oral tid or 500 mg oral tid) in patients with carcinoid syndrome not adequately controlled by ≥30 mg/month of octreotide LAR or ≥120 mg/month of lanreotide autogel.

Radiolabeled somatostatin analogs were in use since 1990s for metastatic somatostatin receptor positive NETs in Europe, but are not FDA approved in the USA due to the lack of randomized prospective trials. They are included in the ESMO (European Society for Medical Oncology) [53] and ENETS (European Neuroendocrine Tumor Society) [54] guidelines. The somatostatin analogs in these modalities help in delivering the therapeutic radionuclides (such as ^{111}In, ^{90}Y, ^{177}Lu, and ^{213}Bi) to the SSTR positive NET cells followed by the internalization of radionuclides and emission of radiation causing cell death. Treatment with radiolabeled somatostatin analogs was shown to have decent antitumor effects, with the second generation β-particle emitting agents (^{90}Y-DOTATOC and ^{177}Lu-DOTATATE) producing 22–35 % partial remissions and 42–62 % stable disease in NETs [55]. A phase III study (NETTER-1; NCT01578239) is presently ongoing, comparing ^{177}Lu-DOTATATE plus best supportive care (30 mg octreotide LAR) with high dose (60 mg) octreotide LAR, in midgut NET patients who have progressed while on a standard dose of octreotide LAR at baseline.

In well-differentiated NET patients who have achieved initial tumor control with long acting SSAs given every 4 weeks, the efficacy of extended dosing interval (every 6–8 weeks) has not yet been compared to continuing conventional dosing interval. This extended dosing interval has been studied in Acromegaly and was shown to be safe and cost-effective [56, 57]. Longer acting SSA formulations, which could be given every 3 months, are currently in development.

Conclusion

PROMID and CLARINET studies established the antitumor activity of 30 mg octreotide LAR and 120 mg lanreotide autogel in well- or moderately-differentiated metastatic NETs, respectively. Both of them were shown to be beneficial in the management of carcinoid symptoms as well. Although octreotide LAR is FDA approved for carcinoid symptom control and lanreotide autogel is approved for antiproliferative effect, both of them are used in clinical practice for either symptom control or as antitumor agents in symptomatic or asymptomatic unresectable neuroendocrine tumors. However, doses greater than the recommended dosing may be needed for octreotide LAR in better symptom and tumor control. The use of lanreotide autogel for refractory carcinoid symptoms or disease progression on conventional octreotide LAR may be more cost-effective in clinical practice, compared to using higher doses of octreotide LAR. Newer SSAs, oral small-molecule inhibitors of peripheral serotonin synthesis, and radiolabeled somatostatin analogs are currently being studied in NET patients who are no more responsive to conventional doses of octreotide.

Compliance with Ethical Standards

Conflict of Interest Venkata K. Pokuri declares that he has no conflict of interest. Mei Ka Fong participated in the advisory panel for lanreotide (Ipsen Pharmaceuticals) without financial compensation. Renuka Iyer has received compensation from Ipsen Pharmaceuticals for service as a consultant and has also received nonfinancial support from Ipsen for the review of manuscript content.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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