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Digital Object Identifier (DOI)
https://doi.org/10.1002/onco.13847

Notes/Citation Information

Published in *The Oncologist*, v. 26, issue 7.

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The Oncologist®

Gastrointestinal Cancer

Opportunities to Improve Symptom Control with Somatostatin Congeners in GEP-NETs: A Review of Key Issues

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Octreotide • Lanreotide • Carcinoid syndrome • Neuroendocrine tumors

Abstract

Octreotide acetate (octreotide) is the most prescribed and most studied somatostatin congener, or analog, for gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and carcinoid syndrome, the latter of which may be characterized by debilitating diarrhea and flushing. Approved in the U.S. more than 30 years ago, octreotide is widely used to control the symptoms of carcinoid syndrome and has been shown to demonstrate antiproliferative activity. The two formulations available in the U.S. include a subcutaneous immediate-release (IR) injection introduced in 1989 and a long-acting repeatable (LAR) intramuscular injection approved in 1999. Lanreotide depot (lanreotide), a more recent somatostatin congener, has been available in the U.S. since 2014.

Despite widespread use of octreotide LAR, several key challenges exist with the current depot-based treatment paradigm. Studies indicate that LAR formulations are associated with continued unmet patient needs, owing in part to a loss of bioactivity over time that may necessitate progressive supplemental treatment with IR octreotide to adequately control symptoms. Clinicians should understand the key differences in the pharmacokinetic profiles of the LAR and IR formulations that may contribute to bioactivity loss and somatostatin receptor desensitization. In addition, there is a need to re-evaluate the role of IR octreotide in combination with depot therapy to provide consistent bioavailability and better control of carcinoid syndrome symptoms.

The purpose of this review is to explore all these issues and to re-establish a rationale for the IR formulation, particularly with respect to novel use cases and its use during the COVID-19 pandemic. ***The Oncologist*** 2021;26:e1171–e1178

Implications for Practice: There is a need to re-evaluate the role of immediate-release octreotide in combination with depot therapy to provide consistent bioavailability and better control of carcinoid syndrome symptoms.

Neuroendocrine Tumors and Carcinoid Syndrome

Pathophysiology and Symptomatology

Neuroendocrine tumors (NETs) of the widely diffused neuroendocrine cell system frequently present substantial diagnostic and therapeutic challenges. Well-differentiated NETs, traditionally known as carcinoid tumors, are the most common type of NET, with an estimated incidence of more than 12,000 U.S. cases annually (6.98 per 100,000 persons in 2012) [1]. The prevalence of NETs is estimated at 175,000 people in the U.S. NETs of gastrointestinal (GI) origin include the appendix and ileum (the most common), the respiratory tract, the genitourinary system, and several organs [2]. Both incidence and prevalence of NETs are rising, and NETs are anticipated to emerge from rare disease status within the next decade [1].

Patients with advanced, functional NETs may experience symptoms related to tumoral secretion of serotonin and peptide hormones, such as gastrin, glucagon, insulin, vasoactive intestinal peptide, and, rarely, somatostatin, parathyroid hormone-related protein, adrenocorticotrophic hormone, growth hormone, and thyroid-stimulating hormone [2]. Most of these tumors are

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malignant and predominantly associated with increased plasma serotonin levels, which drive symptoms in small-bowel tumors [2]. These augmented serotonin levels, as well as increased activity from other potential substances such as histamine, kallikrein, prostaglandins, and tachykinins, may mediate a serious condition called carcinoid syndrome (CS), which manifests as episodic facial flushing; urgent, debilitating diarrhea; and potential development of fatal cardiac valvular fibrosis and mesenteric fibrosis [3, 4]. Carcinoid syndrome is estimated to occur in 30%–40% of patients with well-differentiated GI NETs [5].

Diarrhea secondary to CS occurs in 58%–100% of patients [5]. It tends to be watery after the first or second bowel movement; movement frequency can range from two per day to more than 20 per day [6]. Diarrhea is a multifaceted symptom, driven by stool form, consistency, frequency, and urgency [7], and it can be extremely debilitating, often requiring fluid and electrolyte management [6]. It affects quality of life (QoL) and mental health status and often results in significant changes to patient lifestyle, including diet, work, physical activity, and social life [5]. Patients with CS-induced diarrhea also experience economic challenges [8, 9]. One study found that the mean annual cost to patients with malignant GI NETs was nearly double that of the national average for all cancers (>$70,000 vs. ∼$38,000) [10]. Diarrhea is the primary reason patients seek medical help, which makes effective long-term treatment for this NET condition essential [11]. Early identification and management of symptoms is critical to reducing both disease burden and cost.

Differential Diagnosis

NETs are diagnosed through histological verification of hematoxylin eosin-stained tissue and the presence of the neuroendocrine markers synaptophysin and/or chromogranin A. Neuroendocrine neoplasms are graded according to Ki-67 index and mitotic count. They are clinically classified by both site of origin and hormonal secretion [12]. The use of ^{68}Ga (gallium) and ^{64}Cu (copper) linked to somatostatin analogs and localized with positron emission tomography/computed tomography imaging is increasing and can lead to more accurate tumor staging and preoperative imaging (sensitivity 91%, specificity 94%) [13, 14]. Neuroendocrine neoplasms are typically considered either early (completely resectable) or advanced (unresectable/metastatic) [12].

Impact of Symptoms on Patient QoL

NETs and symptoms associated with CS significantly erode patient QoL. Higher frequency of bowel movements, diarrhea, urgency, fecal incontinence, and cutaneous flushing correlate with decreased QoL, which in turn affects patient work, diet, social life, and physical activity [6, 15].

One survey examined the effect of NET treatment on patient QoL. Patients with recurrent disease reported poorer physical, social, and mental function compared with controls having no current NET. Depression scores between groups were similar; however, patients with recurrent disease reported significantly greater anxiety. The difference in physical functioning between groups was even more striking; patients with recurrent NETs reported notably more fatigue and impaired overall physical function and sleep quality than those with no current NETs [16].

The Role of Somatostatin Analogs in Treating Nets

Guidelines and the Role of Somatostatin Analogs in the Current Treatment Paradigm

Neuroendocrine tumors are highly heterogeneous, and all elements must be considered (e.g., disease burden, symptoms, histopathology, rate of growth) to determine the best course of treatment [13]. Obtaining relief from diarrhea and flushing and achieving biochemical control are fundamental aspects of improving QoL in patients with symptoms of functioning NETs. Because the disease course is often long, symptom management and palliative care are particularly important to preserving QoL [11].

Both the National Cancer Comprehensive Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend surgery as first-line treatment of NETs [13, 17]. However, more than 80% of patients present with advanced, nonresectable disease [11]. In addition, conservative management is often recommended for elderly patients or those with significant comorbidities and lesions ≤2 cm [17, 18]. Beyond surgical intervention, the somatostatin congeners (more commonly known as analogs) octreotide acetate and lanreotide have had the most profound effect on NET management [13, 19].

Somatostatin analogs (SSAs) are standard first-line therapies for functional NETs, according to the NCCN, ESMO, and North American Neuroendocrine Tumor Society (NANETS), and they are generally used to control tumor growth and associated clinical symptoms [13, 17, 20]. Positive somatostatin receptor status is generally required but is not necessarily predictive of response, owing in part to its tendency to miss lesions <1 cm in size. Per NCCN guidelines, SSAs are also indicated in patients with hormonal symptoms [13]. In patients with uncontrolled symptoms, ESMO recommends reducing the injection interval of long-acting SSAs to every 2 or 3 weeks (instead of every 4 weeks) or adding short-acting octreotide. It is worth noting that, despite its addition to the guidelines and common application in clinical practice, increased injection frequency is off label for both octreotide and lanreotide products [17].

Use of SSAs to Manage the Symptoms of CS

In addition to controlling diarrhea and flushing, SSAs are also used to manage other aspects of CS, such as carcinoid heart disease and mesenteric fibrosis [9]. Vasoactive substances produced by NET tumors can induce myofibroblast proliferation and deposition of extracellular matrix within the heart, and local desmoplastic response around the tumor [6, 9]. Results of SSAs, although mechanistically promising, have been mixed. This may be because SSAs only reduce, not eliminate, circulating levels of bioactive substances responsible for fibrosis. More conclusive work is needed to discern the true impact of SSAs on these responses [9].

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Historical Perspective of Somatostatin Analogs and the Evolution of the LAR-Based Treatment Paradigm

The discovery of somatostatin in 1973 provided a new approach to treating diseases such as NETs and acromegaly that are associated with endocrine hypersecretion [21]. In 1989, the U.S. Food and Drug Administration (FDA) approved octreotide acetate subcutaneous (SQ) immediate-release (IR) injection for the treatment of CS and the diarrhea of vasoactive intestinal peptide carcinoma syndrome [19].

In a 1999 study, approval of the LAR intramuscular (IM) formulations (10, 20, and 30 mg once monthly) continued to expand the clinical application of octreotide [22]. The LAR formulation is administered intramuscularly once every 28 days [23]. In 2014, the FDA approved somatuline depot (lanreotide acetate) SQ injection monthly for improvement of progression-free survival in patients with GEP-NETs. Subsequently, in 2017, lanreotide was also approved for treatment of CS to reduce the frequency of short-acting somatostatin analog rescue therapy [24, 25].

A study by Modlin et al. of pooled data from more than 14 trials spanning 20 years ($n = \sim 400$ patients) revealed that 71% of patients with GEP-NETs experienced resolution or improvement of diarrhea (range, 40%–88%) and flushing (range, 485–100%) after treatment with octreotide [26]. Clinical trials also support a reduction in the number of days patients on lanreotide experience diarrhea and/or flushing [27]. However, recent data from a large observational cohort shows that 43% of study subjects still experienced diarrhea after 6 months of lanreotide therapy compared with 44% at baseline [28].

The most common adverse effects associated with SSAs include nausea, abdominal cramps, loose stools, mild steatorrhea (because of meal-stimulated inhibition of pancreatic exocrine secretion and subclinical fat malabsorption), and flatulence. Subclinical fat malabsorption may be exacerbated in the setting of higher fat consumption with daily meals. These symptoms start within hours of the first SQ injection, are dose dependent, and usually spontaneously subside within the first few weeks of treatment. All SSA formulations are well tolerated by most patients [29].

Although octreotide and lanreotide have similar indications, their pharmacokinetics (PK) profiles are dissimilar. Octreotide LAR has a more predictable PK profile than prolonged release lanreotide. The steady-state PK of lanreotide is higher than that of octreotide, which can potentially increase the risk of dose-dependent side effects. However, the lanreotide 120-mg profile has been found to be comparable with the 90-mg profile, which suggests that lanreotide is not strictly dose proportional. The high variability in mean maximum concentration (Cmax) and lack of dose proportionality with lanreotide suggest that uptitrating from 90 mg to 120 mg may not produce a predictable effect or improve efficacy in every patient [23].

Owing to a lack of randomized trials, no data to guide sequencing of the systemic therapy options are currently available [20]. In a recent retrospective administration claims analysis of almost 3,000 patients with NETs, >80% were prescribed octreotide LAR, in part because of its dosing convenience over the IR formulation [18, 29, 30].

Current Use Cases for Octreotide IR

The IR formulation is rarely used alone for long-term therapy but can be particularly effective as rescue therapy in CS patients [11]. Unlike the LAR formulation, which is designed to release the drug over a 28-day period [30], the IR formulation has a short half-life (1.7–1.9 hours) and is immediately bioavailable, permitting administration up to three times a day [31]. Supplemental IR octreotide is required for approximately 2 weeks after octreotide LAR treatment is initiated or until steady-state is achieved. Intermittent rescue IR injections may also be required for rapid relief of acute or breakthrough symptoms [13, 31].

In a single study, ∼30%–40% of patients receiving monthly somatostatin therapy required octreotide rescue medication at 4 weeks to fully control CS symptoms [22]. However, analysis of an administrative claims database showed that only 2% of patients prescribed octreotide filed coverage claims for both LAR and IR formulations [18]. Despite the potential benefits of octreotide IR as rescue therapy, it remains underutilized.

Current Octreotide LAR-Based Treatment Paradigm: Challenges and Opportunities for Clinical Improvement

Areas of Unmet Clinical Need

Despite the breadth of evidence and advances in NET treatment, studies have shown that most of these patients live with significant physical challenges and unmet needs [32]. For instance, ongoing diarrhea is common and most often due to incompletely controlled CS [6]. In a large, international, online survey, 741 with NETs reported fatigue (∼66%), diarrhea (∼48%), sleep disturbance (∼35%), and pain and discomfort (∼40%) as their greatest physical challenges (Fig. 1) [32].

In an online survey of 100 patients with NETs who were currently on SSA therapy, the most frequently reported CS symptoms were diarrhea (90%), flushing (78%), and weight gain/loss (48%). Twenty-nine percent of patients reported daily diarrhea, and 23% experienced daily flushing episodes. Sixty-five percent of patients reported having to stop physical activities, whereas 57% reported difficulty sleeping due to NETs symptoms. Most concerning were the levels of anxiety and depression in patients with NETs, with results showing that 45% of patients were affected and may have needed to seek mental health treatment [33]. These studies indicate that most patients are coping with their disease but need better management of other coassociated symptoms [32].

Receptor Desensitization and Tachyphylaxis

With widespread adoption of the octreotide LAR formulation, clinicians have observed that eventual resistance and tachyphylaxis to octreotide LAR is common, if not inevitable. During long-term therapy, a gradual reduction in sensitivity to octreotide with regard to its clinical effect and inhibitory action on hormone secretion has been reported [34].

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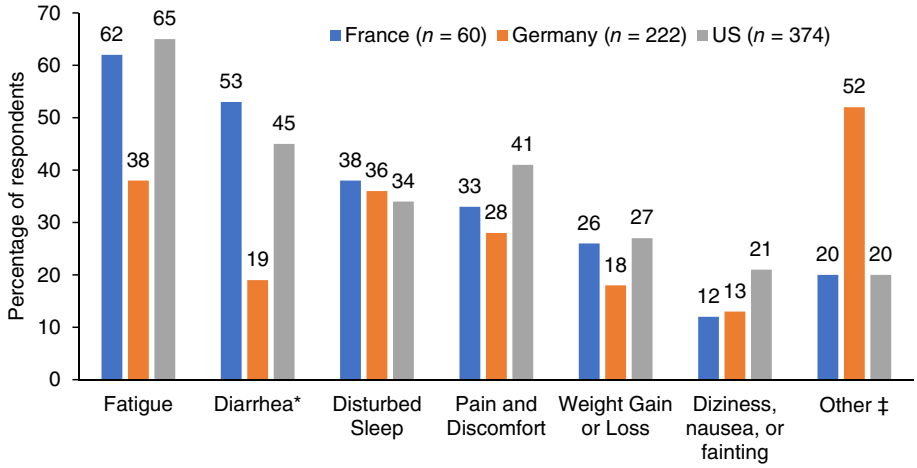

Figure 1. Physical challenges of living with NETs. Proportions of respondents who experienced each challenge in France, Germany, and the US are shown. *Other symptoms include pain, vomiting, and shortness of breath. †No German patients specifically selected "diarrhea," but 20% of those who selected "other" stated that they had diarrhea after an operation. It is unknown whether they experienced diarrhea beforehand. Diarrhea could be caused by consequences of surgery and treatments rather than the disease. Data source: Khan et al [32].

In a study evaluating long-term results of lanreotide depot treatment in malignant CS, 46% of patients experienced loss of symptomatic response and radiologic response at a median 42 months (range, 8–107). Forty-four percent achieved control after a dose increase to 120 mg/28 days. However, 56% of the patients who lost response required additional treatment [35].

Somatostatin receptor 2 (SSTR2) desensitization and lower suppression despite octreotide and lanreotide treatment, particularly in GEP-NETs, has been an important clinical observation [36]. In an open-label, randomized, multicenter study designed to assess two dose levels of octreotide LAR, 124 patients with active or prior chemotherapy-induced diarrhea and scheduled chemotherapy were randomized to receive up to six doses of either octreotide LAR 30 or 40 mg (above-label dose). Both dose levels provided clinical benefit, although fewer patients in the 40-mg group than the 30-mg group experienced severe diarrhea (48.4% vs. 61.7%, $p = .14$), required intravenous (IV) fluid (18.8% vs. 31.7%, $p = .10$), and had diarrhea-related unscheduled health care visits (28.1% vs. 41.7%, $p = .11$). However, no significant differences in QoL or treatment satisfaction were observed between the treatment groups. These results suggest that patients, irrespective of dose, may need rescue therapy with octreotide IR to mitigate receptor desensitization [37].

Attempting Improved Control Through Dose Escalation

The FDA label recommends a starting dose of 20 mg of octreotide LAR, with titration up to 30 mg in patients with suboptimally controlled symptoms [31]. However, in current clinical practice, above-label doses of octreotide LAR are commonly prescribed for patients with metastatic NETs who show suboptimal control of CS or tumor growth while on the maximum label dose of octreotide LAR [38].

Studies have suggested that an above-standard dose of octreotide LAR may improve symptom control among patients who have CS symptoms prior to dose escalation [39]. In current clinical practice, 13%–30% of patients receive above-standard LAR doses in an effort to adequately control symptoms or suppress tumor progression [18, 40]. Similar responses to dose escalation are often discussed with lanreotide therapy in cases of symptomatic and radiologic progression [35].

Often the circulating octreotide drug levels produced by LAR doses 10, 20, or 30 mg/month do not completely saturate SSTR2 receptors in all patients [41]. Chronically undersaturated receptors combined with desensitization mechanisms can increase production of somatostatin receptors, creating an escalating cycle [41].

Higher doses of octreotide LAR comes at increased cost. According to recent estimates, the additional annual costs for above-label dosing range from $5,000 to $40,000 per patient, depending on the amount of octreotide they are given [18]. These costs may be mitigated, and symptom control improved, in part by choosing the appropriate IR formulation to supplement vs increasing the dose.

Limited Bioavailability of LAR Formulations

The octreotide LAR formulation is available in a vial containing the sterile drug product, which, when mixed with the diluent, becomes a suspension administered as a monthly intragluteal injection. Intramuscular injection is not typically 100% bioavailable as it must be absorbed from the muscle over time [42]. Label-reported bioavailability for the LAR formulation is only 60–63%, with a large portion of the drug excreted [30].

Variability in operator skill and experience administering the IM octreotide injection can sometimes pose a challenge. A study of 115 patients evaluated the outcomes of 328 intended gluteal octreotide IM injections. Only 52% of injections were successfully delivered at baseline [43].

Most patients receive LAR as IM injections in the upper outer quadrants of the buttocks. Repeated injections at these sites may be responsible for progressively lower drug

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Table 1. Comparative pharmacokinetics of octreotide LAR and IR

Pharmacokinetic characteristic	LAR, %	IR, %
Bioavailability	25–30	100
Peak-to-trough variation	44–68[a]	163–209[a]

From refs. [31, 41].
[a]When octreotide LAR was administered intramuscular every 4 weeks, the peak-to-trough variation in octreotide concentrations ranged from 44% to 68% compared with the 163% to 209% variation encountered with the subcutaneous 3 times daily regimen of octreotide injection solution [30].
Abbreviations: IR, immediate-release; LAR, long-acting repeatable.

effectiveness, owing to a well-described association between these injections and granulomatous reactions in the gluteal muscle [41].

Another potential factor contributing to decreasing efficacy of the LAR formulation is an unanticipated change in the drug formulation. A change in the size, distribution, or thickness of the microsphere's polymer coating could significantly alter the drug-release characteristics of the LAR preparations [41].

Rationale for Use of Octreotide IR in Current Clinical Practice

Increased Absorption and Bioavailability of IR Formulations

Octreotide is rapidly and completely absorbed after SQ injection. Peak concentrations of 5.2 ng/mL (for a 100-μg dose) were reached 0.4 hours after dosing (Table 1). Using a specific radioimmunoassay, both the IV and SQ doses were deemed to be bioequivalent. Peak concentrations and area under the curve values were dose proportional after IV single doses up to 200 μg, SQ single doses up to 500 μg, and after SQ multiple doses up to 500 μg three times daily (1,500 μg/day) [30].

As expected, the PK of the octreotide IR formulation differ from that of the LAR formulation. These dissimilarities affect blood level concentrations and the medication's clinical effect. When the IR formulation is administered SQ, and absorption is 100%, thus making the drug 100% bioavailable [31, 41]. Because the drug's onset of action is faster, CS symptom relief is quicker.

Octreotide binds with a high affinity to SSTR2 and SSTR5 [44]. For effective pharmacologic activation and symptom control, nearly complete saturation of SSTR2 should occur, with circulating drug levels ∼10 times higher than the dissociation constant (Kd). The binding affinity (Kd, 50% receptor saturation) of octreotide to SSTR2 is ∼1 nM (∼1,000 pg/mL), meaning that octreotide levels within the bloodstream should be ∼10,000 pg/mL. Studies have demonstrated that the 10,000-pg/mL level can be achieved only with the IR formulation of octreotide [41].

Octreotide IR Mimics Natural Somatostatin

The pharmacodynamic properties of octreotide IR are like those of somatostatin, with a wide spectrum of inhibitory effects on pituitary, GI, and pancreatic functions, as well as gut endocrine secretions. Compared with native somatostatin, octreotide is highly resistant to enzymatic degradation and has a prolonged plasma half-life of ∼100 minutes in humans, allowing its use in the long-term treatment of various disease states [45]. The octreotide IR formulation delivers a predictable peak, plateau, and half-life, and it mimics the natural levels of somatostatin in the body, which is a significant difference and advantage over the LAR formulation.

Novel Use Cases for IR Octreotide

Treatment of Breakthrough Symptoms

Patients taking monthly injections of octreotide LAR may experience breakthrough symptoms triggered by certain circumstances. For example, with long-term octreotide LAR or lanreotide depot therapy, vitamin D absorption becomes compromised as a result of prandial inhibition of pancreatic enzyme release. Vitamin D_{25} levels will subsequently decrease and remain low, potentially exposing the patient to a long list of symptoms. For such patients, a trial of rescue octreotide IR taken 30 minutes prior to meals may slow serotonin-induced fat malabsorptive diarrhea. In fact, taking octreotide 30 minutes before a meal along with pancreatic enzymes and a vitamin D supplement at least once daily may slowly improve vitamin D_{25} blood levels [19].

Octreotide IR is effective in symptomatic carcinoid patients anytime serotonin levels rise. Physical exercise or exertion, alcohol consumption, or physical or emotional stress can cause these levels to rise dramatically. Prophylactic or on-demand use of IR therapy can prevent the serotonin surges induced by these events. Medical or dental procedures, as well as intercurrent illnesses may also exacerbate symptoms despite octreotide LAR therapy. Treating these "breakthrough" symptoms with 100–500 μg of octreotide IR SQ every 6 to 12 hours has been shown to provide effective symptom control [19].

Preoperative preparation with SSAs to prevent intraoperative carcinoid crisis has been suggested, primarily for patients with known or high risk of CS. However, it is not currently known what molecules mediate intraoperative crisis. A prospective assessment of biochemical and hemodynamic features of intraoperative crisis failed to identify a rise in serotonin. Outcomes following intraoperative carcinoid crisis were related to prompt identification and management of hemodynamic instability rather than the preoperative preparation [17, 20].

In patients treated with SSAs but experiencing refractory diarrhea, addition of telotristat ethyl can be considered, as it reduces bowel movement frequency. If diarrhea remains uncontrolled, additional treatment options, like narcotics, steroids, or surgical dissection, may be explored. For flushing not adequately controlled by SSAs, tumor debulking or chemoembolization represent viable treatment options [6].

Use as a Supplement to Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-dotatate is often considered to improve symptom control in patients with progressive disease and well-differentiated

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NETs who have detectable SSR expression and adequate bone marrow, renal, and hepatic function [13, 17]. PRRT efficacy may not be durable, however, and it is often followed by additional SSA therapy, as full resolution of CS-related symptoms is rarely achieved [17].

There are theoretical concerns regarding competition between SSAs and PRRT treatment for SSR binding [13]. Therefore, guidelines suggest that long-acting SSAs be interrupted at least 4 weeks before PRRT [17]. Short-acting octreotide can be administered as needed for symptom control up to 24 hours before PRRT administrations. Additionally, when octreotide is used around a cycle of PRRT, it should be given immediately after completion of the cycle to avoid binding competition [13].

Small-Bowel Obstruction

Small-bowel obstruction interferes with food intake and can cause nausea and diarrhea in patients with nonoperable terminal cancer. Palliative care is often paramount to these patients, but antiemetics, steroids, and anticholinergics are often insufficient to control symptoms [46]. Octreotide IR has been shown to help control vomiting, one of the most distressing symptoms experienced by some terminal patients [47].

Clinical trial results for the use of octreotide IR in patients with small-bowel obstruction have been mixed. Early data and open-label, single-arm studies show overwhelming evidence for the benefits of octreotide, especially in patients with gynecologic and urologic cancers [48]. In initial small-scale studies using a continuous infusion of 300 μg/day, vomiting was generally controlled rapidly, with 92.8% patients achieving at least a partial response and 71.4% able to resume oral food intake [49]. However, placebo-controlled studies often find similar improvements in both frequency of symptoms and QoL outcomes between octreotide and placebo-controlled groups [48, 50]. Despite these mixed results, some societal guidelines, like ESMO, recommend administering octreotide IR, either subcutaneously or via continuous infusion, to treat refractory symptoms [51].

Carcinoid Crisis

Carcinoid crisis is a serious and potentially life-threatening condition, caused by the release of large amounts of 5-HT and other vasoactive peptides into circulation. Characterized by hypotension, arrhythmias, and tachycardia, carcinoid crisis can occur spontaneously but can also be triggered by surgery or stress. To prevent carcinoid crisis that could be induced by these latter circumstances, patients often use octreotide IR prophylactically [15]. The ideal administration schedule for octreotide IR to prevent carcinoid crisis remains unknown, but guidelines (ENETS, NANETS, and UKNETS) suggest different octreotide dosing schedules, including pre-, intra-, and/or postoperative, to prevent symptoms [52].

Octreotide IR use during COVID-19

The COVID-19 pandemic has posed challenges for many patients, including those with NETs. Treatment of NETs is a health resource-heavy process. In prepandemic studies, patients with NETs averaged 25.7 outpatient visits and 5.6 inpatient visits annually, with the most common being visits to oncologist offices [18, 53].

In response to governmental regulations and individual health concerns, oncology patient visits dropped dramatically in 2020 and, despite the lifting of stay-at-home orders, oncology service use continues to lag behind 2019 levels [54]. In an observational multicenter study, up to 40% of patients interrupted their therapy over the past year, in part because of the pandemic's impact on in-office visits [55].

An initial report from the Italian Association for Neuroendocrine Tumors reported a significant impact of the COVID-19 pandemic on the number of newly diagnosed cases of NETs, as well as a reduction in surgical procedures and delays in beginning scheduled PRRT.

Although many providers have been able to switch to telemedicine during the pandemic, remote visits preclude administration of octreotide LAR. At-home injections of octreotide IR, combined with telemedicine, can offer patients viable and effective symptom relief and provide clinicians with the opportunity to treat and monitor their patients while also reducing the exposure of both to COVID-19 [56].

Conclusion

Once octreotide steady-state concentrations are achieved, octreotide LAR controls the symptoms of CS at least as well as octreotide IR [22]. However, driven mainly by its PK profile, the IR formulation shows unique advantages in a range of patients who can benefit from the better symptom control not provided by the LAR formulation alone. Supplemental use of octreotide IR is consistent with current and emerging NETs clinical practice guidelines [13, 17, 20]. Simulated steady-state profiles suggest that LAR octreotide therapy could be optimized by using octreotide IR to meet individual patient needs, thereby improving both patient experience and clinical outcomes [23].

Acknowledgments

We would like to thank Hospicom, Inc., for editorial support. L.B.A. and T.M.O.'s efforts are partially funded by Sun Pharmaceuticals Inc., an NCI Cancer Center Support Grant (P30 CA177558, L.B.A.), and the University of Iowa Specialized Program of Research Excellence (P50 CA174521, T.M.O.). We also wish to thank Donna Gilbreath of the U.K. Markey Cancer Center's Research Communications Office for assistance with the preparation of this manuscript.

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Data analysis and interpretation: Lowell B. Anthony, Thomas M. O'Dorisio
Manuscript writing: Lowell B. Anthony, Thomas M. O'Dorisio
Final approval of manuscript: Lowell B. Anthony, Thomas M. O'Dorisio

Disclosures

Lowell B. Anthony: Sun Pharmaceuticals (RF); **Thomas M. O'Dorisio:** Sun Pharmaceuticals (RF).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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