Journal of Gastroenterology and Hepatology
JGHF
doi:10.1111/jgh.16638

REVIEW ARTICLE

Gastrointestinal side effects of somatostatin analogs in neuroendocrine tumors: a focused review

Matteo Marasco,*,† Elisabetta Dell'Unto,* Alessandro Laviano,‡ Davide Campana§ and Francesco Panzuto*

*Department of Medical-Surgical Sciences and Translational Medicine, Sapienza University of Rome, Digestive Disease Unit, ENETS Center of Excellence, Sant'Andrea University Hospital, †PhD in Translational Medicine and Oncology, Sapienza University of Rome, ‡Department of Translational and Precision Medicine, Sapienza University of Rome, Clinical Nutrition Unit, Sant'Andrea University Hospital, Rome, §Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum – University of Bologna, Medical Oncology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

Key words
adverse drug events, exocrine pancreatic insufficiency, malnutrition, neuroendocrine tumors, somatostatin analogs.

Accepted for publication 16 May 2024.

Correspondence
Francesco Panzuto, Department of Medical-Surgical Sciences and Translational Medicine, Sapienza University of Rome, Digestive Disease Unit, ENETS Center of Excellence, Sant'Andrea University Hospital, Via di Grottarossa 1035, 00189 Rome, Italy.
Email: francesco.panzuto@uniroma1.it

Declaration of conflict of interest: The authors declare no conflict of interest.
Author contribution: Conceptualization: FP. Writing—original draft preparation: FP, MM, and AL. Writing—reviewing and editing: FP, MM, AL, DC, and ED.
Financial support: This research received no external funding.

Abstract

Neuroendocrine tumors (NETs) are a group of well-differentiated heterogeneous neoplasms characterized by slow progression and distinct clinical and biological behavior. In the majority of patients with NET, first-line treatment is represented by somatostatin analogs (SSAs) that, despite being drugs with high tolerability (even at high doses) and providing to carcinoid symptoms control and anti-proliferative effects, may present some side effects, with potential impact on quality of life and nutritional status. The most frequent side effects are represented by gastrointestinal events in particular alterations in bowel habits (diarrhea and constipation), abdominal pain, exocrine pancreatic insufficiency, and cholelithiasis. Considering the relative rarity of NETs, literature about frequency and standard clinical management of adverse events SSA-related is still lacking and heterogeneous. The aim of this review is to arm gastroenterologists and other physicians treating NET patients with essential knowledge on the side effects of SSAs. By identifying and managing these adverse events early, healthcare professionals can offer optimal care, avert foreseeable complications, and ensure the best outcomes for patients. Without such early recognition, there is a risk of diminishing the patient's quality of life and their ability to sustain treatment over time.

Introduction

Neuroendocrine neoplasms (NENs) represent a diverse group of neoplasms arising from neuroendocrine cells throughout the body. They are clinically heterogeneous, ranging from indolent slow-growing tumors to highly aggressive rapidly progressive forms. Recent epidemiological data indicate a steadily increasing incidence of NENs globally, a trend attributed partly to enhanced diagnostic techniques and heightened clinical awareness.[1]

Pathologically, NENs are graded based on mitotic count and Ki-67 proliferation index, both crucial factors in determining the tumor's aggressiveness and in guiding therapeutic strategies. The World Health Organization (WHO) classification system categorizes NENs as well-differentiated neuroendocrine tumors (NET) G1, G2, and G3 and neuroendocrine carcinomas (NEC) based on these histological features. Grade 1 NETs are defined by a mitotic count of less than 2 per 10 high power fields (HPF) and/or <3% Ki-67 index; Grade 2 NETs have a mitotic count of 2–20 per 10 HPF and/or 3–20% Ki-67 index; and Grade 3 NETs exhibit a mitotic count of more than 20 per 10 HPF and/or >20% Ki-67 index.[2] Neuroendocrine carcinomas are characterized by a poorly differentiated morphology, usually with high Ki-67 value. Grading, along with tumor burden and primary tumor site, represents the strongest prognostic factor affecting prognosis and clinical outcome in NEN patients.[3]

Since the majority of NENs are asymptomatic, they often reach an advanced stage by the time of initial diagnosis, leaving physicians with limited options for curative intervention and necessitating systemic medical treatment. This is particularly common for small bowel and pancreatic NENs. In contrast, gastric and rectal primaries usually follow a more indolent course and, as a result, are less frequently diagnosed at an advanced stage.[1]

The therapeutic landscape for NENs is complex and multifaceted, involving a range of treatment modalities. Alongside somatostatin analogs (SSAs), targeted therapies such as everolimus and sunitinib, peptide receptor radionuclide therapy (PRRT), and various chemotherapy regimens play integral roles in the management of these tumors.[4] This variety of treatment options reflects the diverse nature of NENs and underscores the need for personalized

treatment approaches tailored to individual patient characteristics and tumor profiles. However, as the majority of NENs are slow-growing, well-differentiated NETs, SSAs are considered the first-line treatment and form the basis for treating these patients at the beginning of their clinical history.[4]

Focus of the review

This review will specifically focus on the tolerability of SSAs, with a particular emphasis on adverse events involving the digestive system. The intent is to provide gastroenterologists and other clinicians with practical clinical insights for identifying and managing gastrointestinal side effects in patients with NENs receiving SSA therapy. Through this focused approach, the review aims to contribute valuable knowledge to enhance patient care and improve treatment outcomes in this patient population.

In this narrative review, we gathered data by conducting a comprehensive search of the MEDLINE database without imposing any date limitations. Our search criteria were centered around specific keywords, namely, "neuroendocrine tumors," "somatostatin analogs," and "side effects." The scope of our inclusion was limited to articles that were pertinent to the aims of this review and composed in English. It is important to note that this research did not adhere to the systematic review protocol; instead, the selection of articles was based on the subjective judgment of the authors.

SSAs: biological effects and efficacy

SSAs, such as octreotide and lanreotide, represent critical therapeutic agents in the management of NETs. These synthetic versions of the natural hormone somatostatin exhibit enhanced potency and an extended duration of action compared to their natural counterpart. Octreotide is available in two forms: a short-acting version for subcutaneous or intravenous use and a long-acting release (LAR) variant administered intramuscularly at 30 mg every 4 weeks. Lanreotide Autogel®, on the other hand, is a depot formulation available in doses of 60, 90, and 120 mg. It is given subcutaneously at 120 mg every 4 weeks and achieves steady-state concentration on the first day. They are particularly effective in inhibiting the secretion of various hormones and peptides by neuroendocrine cells, providing significant relief in symptoms associated with functional NETs that produce excess hormones.

Apart from their role in symptom control, SSAs have also demonstrated notable antiproliferative actions on certain types of well-differentiated, slow-growing NETs.[5,6] By inducing cell cycle arrest, these agents can potentially reduce tumor growth. This is further complemented by their ability to reduce tumor blood flow and interact with various growth factors and cellular signaling pathways, possibly impacting tumor progression and metastasis.[7]

The efficacy of octreotide in prolonging progression-free survival was initially demonstrated in the PROMID study where the median time to tumor progression in patients treated with octreotide LAR was 14.3 months compared to 6 months in the placebo group. This highlighted a significant antiproliferative effect, with a 66% stabilization rate observed after 6 months of treatment.[5]

Similarly, lanreotide has shown significant efficacy in improving progression-free survival in patients with metastatic enteropancreatic NETs enrolled in the CLARINET trial. This randomized double-blind study demonstrated that the risk of disease progression within 96 weeks was reduced by 53% with lanreotide, as compared to placebo. This was reflected in the estimated 24-month progression-free survival rates of 65.1% in the lanreotide group versus 33.0% in the placebo group.[6] The study included both G1 and G2 tumors, although with Ki-67 $< 10\%$.

In the real-world setting, the study from the Spanish R-GETNE registry on SSAs for metastatic GEP-NETs analyzed 535 patients.[8] It found that both octreotide LAR and lanreotide autogel were similarly effective in extending PFS, with median values of 28.0 and 30.1 months, respectively. This indicates that both treatments are viable options for well-differentiated, metastatic GEP-NETs, aligning with results from randomized clinical trials.

These studies affirm the clinically relevant antiproliferative effects of long-acting SSAs in patients with NETs, providing a strong basis for their use in clinical practice.

SSA tolerability

Octreotide and lanreotide are highly tolerated, making them preferred treatments for NETs. Most adverse effects associated with these drugs are mild to moderate in severity and can be effectively managed in clinical settings. This excellent tolerability is a significant factor in their widespread use and acceptance in the management of NETs. SSAs can lead to gastrointestinal disturbances such as diarrhea, constipation, abdominal cramps, and nausea. They may also cause gallstone formation due to reduced gallbladder motility. Additionally, long-term use of these drugs might contribute to fat malabsorption and nutritional deficiencies.

Abdominal symptoms. Patients receiving SSAs frequently experience gastrointestinal side effects, which are generally mild to moderate. It is estimated that SSAs increase the risk of gastrointestinal symptoms in NET patients by 57%.[9] Common abdominal symptoms include:

- Diarrhea: A significant proportion of patients report this symptom. In the CLARINET study[6] and the control group of the RADIANT-2 trial receiving octreotide LAR,[10] diarrhea was identified as one of the most common adverse events, experienced by 26% and 16% of patients, respectively. When asked, 78% of patients reported the presence of diarrhea while receiving SSA treatment.[11] This is noteworthy as diarrhea is also a primary symptom of carcinoid syndrome, complicating the identification of diarrhea as a side effect of SSA treatment. This complexity underscores the necessity of a monitoring protocol to distinguish between symptoms of the underlying disease and side effects of the treatment.[12] In cases of diarrhea related to suspected uncontrolled carcinoid syndrome, the first choice is to increase the dose of SSAs by shortening the interval between administrations of long-acting compounds and/or by adding daily short-acting subcutaneous octreotide. If ineffective, a multidisciplinary discussion is mandatory to explore changes in systemic therapy management (e.g. adding telotristat, planning PRRT, proposing liver-directed ablative therapies).[13] Conversely, if diarrhea does not appear to be related to carcinoid syndrome, exocrine pancreatic insufficiency (EPI)

should be considered (refer to the chapter below). Symptomatic therapy using loperamide should be considered when both uncontrolled carcinoid syndrome and EPI have been excluded.

- Constipation: While diarrhea is more commonly associated with SSA treatment, a significant number of patients may conversely experience constipation. In fact, 85% of respondents in the survey by Whyand *et al*. reported experiencing constipation.[11] This contrasts with typical reports of diarrhea risk and emphasizes the need for greater awareness among healthcare professionals and patients about the broader range of potential side effects, including constipation. Since there are no data on the specific treatment of SSA-related constipation, supplementary fiber intake, adequate hydration, and the use of PEG are recommended approaches for these patients, as indicated for treating idiopathic chronic constipation[14] (Fig. 1).
- Other abdominal symptoms: Abdominal cramps are another common symptom, often impacting patients' daily activities. In patients receiving SSAs, there has also been a reported increased risk of 76% for experiencing nausea, which is sometimes associated with vomiting.[9] Anorexia has also been reported, although it is rare (Table 1).

EPI. EPI is a significant side effect in patients with NETs treated with SSA. This condition arises from the inhibitory effect of SSAs on pancreatic exocrine function, leading to reduced secretion of digestive enzymes, resulting in symptoms like steatorrhea, weight loss, and malabsorption of lipids and liposoluble micronutrients. These symptoms can significantly impact patients' quality of life (QoL) and lead to serious complications.

The prevalence of EPI in patients treated with SSAs is notable. It has been reported that EPI rate is approximately 20–24% in patients receiving long-term SSAs treatment.[15–17] These studies indicate that EPI is relatively common yet often underdiagnosed due to overlapping symptoms with other gastrointestinal disorders and the complexity of the clinical presentation of NETs.

A recent study by Hall *et al*. utilizing the 13C-mixed triglyceride breath test (13C-MTGT) revealed significant reductions in exocrine function following SSA therapy.[18] This study demonstrated that the 13C-MTGT is a valuable tool in early detection of EPI in NET patients treated with SSAs. According to Hall's findings, there was a median reduction of exocrine function from baseline of −23.4% in all patients after commencing SSAs therapy.

According to a meta-analysis that included 428 cases of EPI and 673 controls comparing the accuracy of fecal elastase-1 (FE-1) to the secretin stimulation test, a pooled sensitivity of 0.77 (95% CI 0.58–0.89) and a specificity of 0.88 (95% CI 0.78–0.93) for FE-1 were reported.[19] When compared to quantitative fecal fat estimation in 345 cases of EPI and 312 controls, FE-1 showed a pooled sensitivity of 0.96 (95% CI 0.79–0.99) and specificity of 0.88 (95% CI 0.59–0.97). These findings suggest that FE-1 is a highly sensitive and specific test for the detection of EPI, particularly in patients with a high pretest probability of the condition.[19]

The management of EPI involves treatment with pancreatic enzyme replacement therapy (PERT). If left untreated, EPI can result in complications related to fat malabsorption and malnutrition, having a negative impact on QoL. PERT formulations, all derived from porcine sources, are equally effective at equivalent doses. The initial PERT treatment should be at least 40 000 USP units of lipase during each meal in adults, with subsequent dosage adjustments based on meal size and fat content.[20]

A study focused on pancreatic cancer patients highlighted that PERT, when used appropriately with all meals and snacks, significantly alleviates symptoms such as indigestion, light-colored or orange stools, and visible food particles in stool.[21] Patients taking PERT with meals also reported weight gain and less weight loss. This underscores the importance of appropriate PERT usage and administration, which is crucial for symptom alleviation and improving patients' QoL.

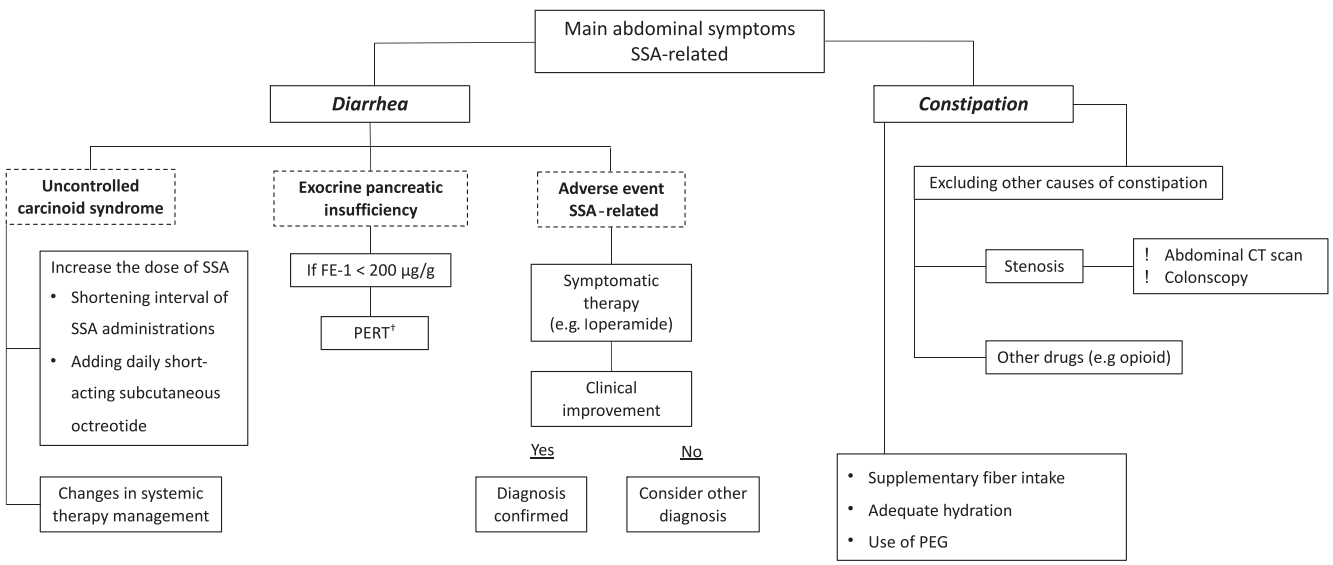

Figure 1 Main abdominal symptom management in patients with NET in SSA treatment. †See Figure 2; PEG, polyethylene glycol.

Table 1 Main digestive adverse effects related to SSA treatment

Side effect	Rate	Management
Abdominal symptoms	57%	
Diarrhea	16–26%[†]	Differential diagnosis (e.g. uncontrolled carcinoid syndrome, EPI)
	78%[‡]	Symptomatic therapy (e.g. loperamide)
Constipation	85%[‡]	Supplementary fiber intake, adequate hydration, use of PEG
Nausea	76%	Symptomatic therapy (e.g. metoclopramide)
Abdominal cramps	50%	Symptomatic therapy (e.g. scopolamine)
Cholelithiasis	5–60%	Prophylactic cholecystectomy (in patients undergoing for primary GI-NET surgery)
		Ursodeoxycholic acid
Exocrine pancreatic insufficiency	20–24%	PERT
		Nutritional status monitoring
		Low–moderate fat diet and frequent smaller meals

[†]CLARINET[6] and RADIANT-2[10] studies.
[‡]Self-reported.[11]
PEG, polyethylene glycol; PERT, pancreatic enzyme replacement therapy.

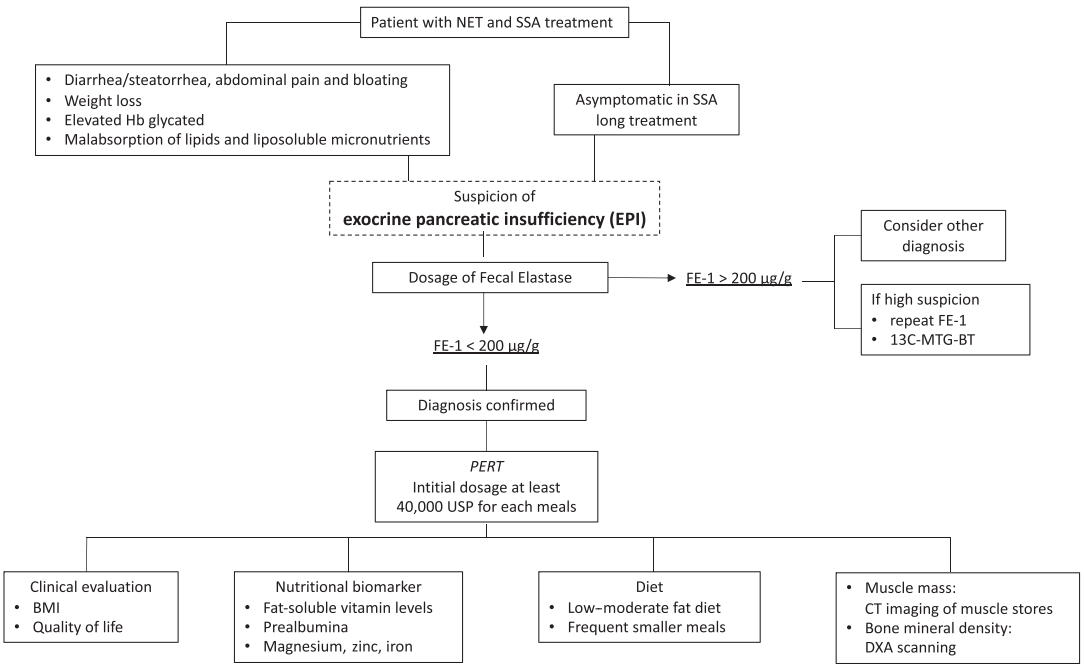

Figure 2 Exocrine pancreatic insufficiency management. 13C-MTG-BT, 13C-mixed triglyceride breath test; DXA, dual energy x-ray absorptiometry; FE-1, fecal elastase; PERT, pancreatic enzyme replacement therapy.

Routine supplementation and monitoring of fat-soluble vitamin levels are crucial in managing EPI.[20] Dietary modifications should include a low–moderate fat diet with frequent smaller meals, avoiding very-low-fat diets. Successful treatment with PERT is indicated by a reduction in steatorrhea and associated gastrointestinal symptoms, a gain in weight, muscle mass, and muscle function, and improvement in fat-soluble vitamin levels. Monitoring EPI and obtaining baseline measurements of nutritional status, including body mass index and quality-of-life measures, is recommended, along with periodic dual-energy x-ray absorptiometry scans.[20]

Elevated glycated Hb levels were found to be significantly associated with an increased risk of EPI.[22] Routine FE-1 dosage should be planned, along with other laboratory tests during follow-up, to diagnose this relevant condition early, which may deteriorate the QoL and cause malnutrition (Fig. 2). Awareness about EPI diagnosis and treatment should be increased among the multidisciplinary community of physicians dealing with NETs.

Additionally, there is a need for comprehensive reporting of side effects like EPI in clinical trials investigating SSAs efficacy in NET patients. EPI is often not thoroughly understood or actively sought out in these patients, which may lead to incomplete data

regarding the safety profile of SSAs. This lack of comprehensive reporting on side effects such as EPI underscores the need for a more holistic approach in clinical trials, ensuring that all potential adverse effects, especially those indirectly related to the primary treatment outcomes, are adequately monitored and reported.

Cholelithiasis. SSA treatment may be associated with the development of biliary stone disease. The pathogenesis of gallstone disease in patients treated with SSAs involves several mechanisms that impair gallbladder emptying and induce the formation of supersaturated bile. It has been proposed that octreotide alters hepatic bile composition, induces gallbladder stasis, and increases concentrations of various components like calcium, bilirubin, protein, and lipids in gallbladder, heightening the risk of cholesterol and calcium bilirubinate precipitation.[23,24] The incidence of gallstone disease is notably increased in patients treated with SSAs compared to the general population.

One of the oldest reports of gallstone formation in patients treated with SSAs, specifically octreotide, was published in 1997.[25] This study focused on the incidence and morbidity of cholelithiasis in patients with metastatic carcinoid or malignant pancreatic islet cell tumors receiving chronic octreotide therapy. It found a 52.3% overall incidence of cholelithiasis and/or gallbladder sludge across all treatment groups, with a smaller percentage of patients developing symptomatic gallbladder disease. This landmark study underlined the necessity for monitoring gallstone development in patients on chronic octreotide treatment while suggesting that prophylactic cholecystectomy was not generally indicated unless performed in conjunction with other abdominal surgeries.

The development of gallstones during treatment with SSAs was initially reported in acromegalic patients. A retrospective survey covering the last 20 years in tertiary referral centers revealed that among acromegalic patients treated with SSAs, there was a prevalence of 8.3% of gallstones at diagnosis, with an additional 35% developing gallstones during SSAs treatment.[26] Gallstones, microlithiasis, sediment, and sludge variably occurred during SSA treatment, with incidences ranging from 5% to 60% in different studies. However, in most cases, these biliary tract diseases were symptomless and did not require surgery.

Focusing on studies evaluating patients with NETs, a retrospective observational study reported that the incidence of gallstones in patients receiving SSA treatment can be as high as 36.6%, with a mean yearly incidence of 8.73%.[27] In patients with gallbladder in situ, the development of gallstones during SSAs therapy is a significant concern. The European Association for the Study of the Liver (EASL) guidelines recognize patients treated with SSAs as a high-risk group for developing gallstone disease. However, current clinical recommendations on prophylactic cholecystectomy and ursodeoxycholic acid treatment are based on limited evidence from small studies.[28]

A multicenter study conducted a retrospective analysis of patients with NETs treated with SSAs at seven Italian centers from 1995 to 2017.[29] It found that 27.0% of patients developed biliary stone disease, and among them, 27.9% developed biliary complications. Primary gastrointestinal NET and related surgery were identified as independent risk factors for the development of biliary stone disease in SSA-treated patients. Prophylactic cholecystectomy was suggested for patients undergoing surgery for primary GI-NETs, while the role of prophylactic ursodeoxycholic acid in preventing gallstones in SSA-treated patients was not conclusive.

The study by Norlén *et al*. performed in midgut (mostly small bowel) NET patients suggests that concomitant prophylactic cholecystectomy during laparotomy may be recommended in patients with midgut NETs who are planned to undergo treatment with SSAs.[30] This recommendation becomes stronger if the patient has liver metastases and is planned to undergo treatments like radiofrequency ablation or hepatic artery embolization. However, a surgical evaluation is required, and if a complicated cholecystectomy is anticipated, it may be wiser to leave the gallbladder in situ, especially if the patient is not planned for laparotomy.

Most of the available data on gallstone formation in patients treated with SSAs are derived from studies involving patients with acromegaly. Limited data are available on the incidence and management of gallstones in patients with NETs, highlighting a need for more focused research in this specific patient group.

Tolerability of high-dose SSAs

The evidence supporting the use of high-dose somatostatin analogs (HD-SSAs) in treating NET primarily comes from retrospective studies and a limited number of small prospective trials. These studies suggest potential benefits of HD-SSAs in alleviating symptoms and delaying disease progression, but the lack of large-scale, randomized controlled trials means that definitive conclusions about their effectiveness cannot yet be drawn. Different strategies for administering HD-SSAs are explored, such as adjusting the dose frequency (dose density) and the actual dose amount (dose intensity).[31]

A meta-analysis that included 11 studies with 783 patients revealed that the incidence density ratio for new disease progressions was 62 per 100 patients treated with HD-SSAs annually, and the disease control rate stood at 45%. However, these results exhibited significant heterogeneity, which affects the reliability of these findings.[32]

The CLARINET FORTE study, a significant phase 2 trial, involved 99 patients with progressive midgut or pancreatic NETs unresponsive to standard-dose lanreotide.[33] Participants were given an intensified lanreotide regimen (120 mg every 14 days), with different treatment durations for the midgut (up to 96 weeks) and pancreatic NET cohorts (up to 48 weeks). The study reported a median PFS of 8.3 months in the midgut cohort and 5.6 months in the pancreatic NET cohort. The NETTER-1 trial, with its control arm receiving high-dose long-acting octreotide (60 mg every 28 days), similarly reported a median PFS of 8.4 months.[34]

Regarding safety, increasing SSA doses does not appear to adversely affect the safety profile. In the NETTER-1 trial's control arm, no new or unexpected adverse events were reported. Similar results have also been reported from recent data related to the NETTER-2 trial, which investigated the efficacy of PRRT versus high-dose octreotide in a first-line setting in patients with G2–G3 GEP-NET. It confirmed that the most common adverse events with high-dose octreotide were diarrhea, abdominal pain, and nausea, in agreement with what is already known from the existing literature.[35] The CLARINET FORTE study also confirmed a manageable safety profile, with 94.1% of midgut cohort patients and 85.4% of pancreatic NET cohort patients experiencing treatment-emergent adverse events, most of which were mild or moderate.[33] About half of the midgut cohort and over a third of

the pancreatic NET cohort had treatment-related adverse events, mainly diarrhea and abdominal pain. While 18.2% of patients experienced serious adverse events, none of these, including three deaths in the midgut cohort, were linked to the treatment by the investigators. This finding aligns with a real-world study on HD-SSAs, where adverse events were noted in only 15% of patients, predominantly mild, and did not lead to treatment discontinuation. This study also reported that 19% of patients experienced a mild to moderate rise in serum glucose levels, without any severe hyperglycemia cases.[36] Overall, the diverse studies consistently demonstrate that the safety profile of HD-SSAs is comparable to that of standard doses. While the true efficacy of HD-SSAs is yet to be conclusively established, it is evident that increasing the dosage does not necessarily lead to an increase in significant gastrointestinal side effects.

Malnutrition in NET patients

Malnutrition in patients with NET represents a critical aspect of patient care that demands attention from physicians. Its impact on patient outcomes necessitates a comprehensive understanding and approach. Laing *et al*. observed a significant reduction in the prevalence of malnutrition, halving it within 6months post-diagnosis. This suggests that improved control of the tumor and its symptoms may enhance nutrient utilization.[37] Malnutrition is associated with a reduced QoL, as assessed by various validated tools. In patients with NET, the disease course is marked by multiple symptoms. While controlling one or a few symptoms may improve certain quality-of-life domains, this does not necessarily translate to a global improvement.[37] This evidence underscores the necessity for a multi-professional and multidisciplinary approach in treating patients with NET. Beyond affecting patients' lives, malnutrition worsens their ability to withstand the metabolic and functional demands of the tumor and associated therapies. As observed in patients with solid tumors, those with NET who are malnourished experience longer hospital stays compared to their well-nourished counterparts.[38]

Similar to observations in patients with solid cancer, malnutrition in NET patients is marked by muscle mass loss, leading to sarcopenia. A recent report indicates a high prevalence of sarcopenia in patients with digestive tumors, nearing 90%.[39] The pathogenesis of sarcopenia is multifaceted, involving poor nutrient digestion and absorption, an increased inflammatory response, and reduced mobility in patients. The importance of investigating body composition in NET patients, especially during follow-up, is underscored by the detrimental impact of sarcopenia on clinical outcomes. Although no direct correlation between body composition at diagnosis and overall or specific mortality has been established, changes in muscle density during follow-up (such as an increase in low-density muscle and a decrease in normal-density muscle, indicating sarcopenia) are independently linked to overall and tumor-caused mortality.[40]

QoL with SSAs

QoL in patients with NETs is profoundly affected by gastrointestinal symptoms, which are common in functioning tumors, and by the side effects of treatments like SSAs. These factors necessitate the use of specific tools to assess QoL accurately. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Gastrointestinal NETs (EORTC QLQ-GINET21) is a widely used instrument, specifically addressing the unique challenges faced by NET patients.[41] This questionnaire's detailed approach is crucial for tailoring treatment decisions to enhance the overall QoL.

SSAs can have a dual impact on QoL. They may cause gastrointestinal side effects such as diarrhea, abdominal pain, constipation, and vomiting, potentially reducing QoL. Conversely, they can improve QoL by reducing tumor-related syndromes in functioning tumors and mitigating clinical deterioration due to tumor progression. SSAs are among the least toxic treatments and have been proven effective in restoring health-related quality of life (HRQoL) in NET patients.[42] The PROMID study's post hoc analysis using the EORTC QLQ-C30 questionnaire showed that long-acting octreotide significantly enhanced HRQoL compared to placebo, particularly in mitigating fatigue, pain, and insomnia.[43]

Further research, such as a study on metastatic small-intestinal NET patients undergoing SSAs treatment, revealed that despite significant symptoms, patients maintained a high perceived QoL, with minor improvements over a year.[44] This study underlines the importance of consistent symptom monitoring and vitamin level assessments in NET patients receiving SSAs therapy.

Another study by Adams *et al*. involving 120 patients, mainly female with GI primary tumors, undergoing SSA treatment, highlighted the varied impact of SSAs on HRQoL. The PROMIS-29 HRQoL assessment showed overall worse scores compared to the general population, with notable struggles in depression, anxiety, fatigue, insomnia, and social role dissatisfaction. However, most patients still found their lives meaningful, illustrating the complex nature of SSA treatment on QoL.[45]

While SSA treatment for NETs can lead to both physical and psychological challenges, it also offers significant benefits in terms of symptoms control and QoL maintenance. The intricate balance between managing side effects and enhancing QoL underscores the need for comprehensive, patient-centered care in this context.[46]

Conclusions and key messages

Despite the rarity of NETs, their rising incidence coupled with their typically slow progression suggests that gastroenterologists will increasingly participate in patient management. This role extends beyond being a NET specialist in a multidisciplinary team at a referral center but also extends to providing expertise in managing the side effects associated with SSAs. These drugs are the primary treatment for most patients with NETs and are often used over extended periods. Gastroenterologists are likely to encounter clinical scenarios involving symptomatic management of abdominal issues, alterations in bowel habits (such as diarrhea or constipation), EPI, and the development of cholelithiasis. Prompt identification and meticulous handling of these potential side effects of SSAs can enhance the care of patients with NETs who are receiving these treatments, thereby improving the quality of multidisciplinary patient care.

References

1 Dasari A, Shen C, Halperin D *et al*. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol.* 2017; **3**: 1335.

2 Rindi G, Mete O, Uccella S *et al*. Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocr. Pathol.* 2022; **33**: 115–54.
3 Panzuto F, Merola E, Pavel ME *et al*. Stage IV gastro-entero-pancreatic neuroendocrine neoplasms: a risk score to predict clinical outcome. *Oncologist* 2017; **22**: 409–15.
4 Cives M, Strosberg J, Pelle' E, Strosberg J. Emerging treatment options for gastroenteropancreatic neuroendocrine tumors. *J. Clin. Med.* 2020; **9**: 3655.
5 Rinke A, Müller HH, Schade-Brittinger C *et al*. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. *J. Clin. Oncol.* 2009; **27**: 4656–63.
6 Caplin ME, Pavel M, Ćwikła JB *et al*. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N. Engl. J. Med.* 2014; **371**: 224–33.
7 Faggiano A. Long-acting somatostatin analogs and well differentiated neuroendocrine tumors: a 20-year-old story. *J. Endocrinol. Invest.* 2024; **47**: 35–46.
8 Jimenez-Fonseca P, Carmona-Bayonas A, Lamarca A *et al*. External validity of somatostatin analogs trials in advanced neuroendocrine neoplasms: the GETNE-TRASGU study. *Neuroendocrinology* 2021; **112**: 88–100.
9 Wu Q, Chen B, Yan G, Yang Z, Xiong L, He J. A systematic review and meta-analysis of gastrointestinal events associated with nonoperative therapies for neuroendocrine tumors. *Onco. Targets. Ther.* 2018; **11**: 7655–68.
10 Pavel ME, Hainsworth JD, Baudin E *et al*. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011; **378**: 2005–12.
11 Whyand T, Bouvier C, Davies P. Prevalence of self-reported side effects in neuroendocrine tumour patients prescribed somatostatin analogues. *Br. J. Nurs.* 2018; **27**: 738–44.
12 Pusceddu S, Rossi RE, Torchio M *et al*. Differential diagnosis and management of diarrhea in patients with neuroendocrine tumors. *J. Clin. Med.* 2020; **9**: 2468.
13 Grozinsky-Glasberg S, Davar J, Hofland J *et al*. European Neuroendocrine Tumor Society (ENETS) 2022 guidance paper for carcinoid syndrome and carcinoid heart disease. *J. Neuroendocrinol.* 2022; **34**.
14 Chang L, Chey WD, Imdad A *et al*. American Gastroenterological Association-American College of Gastroenterology clinical practice guideline: pharmacological management of chronic idiopathic constipation. *Gastroenterology* 2023; **164**: 1086–106.
15 Lamarca A, McCallum L, Nuttall C *et al*. Somatostatin analogue-induced pancreatic exocrine insufficiency in patients with neuroendocrine tumors: results of a prospective observational study. *Expert Rev. Gastroenterol. Hepatol.* 2018; **12**: 723–31.
16 Saif MW, Larson H, Kaley K, Shaib W. Chronic octreotide therapy can induce pancreatic insufficiency: a common but under-recognized adverse effect. *Expert Opin. Drug Saf.* 2010; **9**: 867–73.
17 Rinzivillo M, De Felice I, Magi L, Annibale B, Panzuto F. Occurrence of exocrine pancreatic insufficiency in patients with advanced neuroendocrine tumors treated with somatostatin analogs. *Pancreatology* 2020; **20**: 875–9.
18 Hall LA, Powell-Brett S, Thompson O *et al*. Casting a wider NET: pancreatic exocrine insufficiency induced by somatostatin analogues among patients with neuroendocrine tumours? *Cancers* 2023; **15**: 1933. https://doi.org/10.3390/cancers15071933
19 Vanga RR, Tansel A, Sidiq S, El-Serag HB, Othman MO. Diagnostic performance of measurement of fecal elastase-1 in detection of exocrine pancreatic insufficiency: systematic review and meta-analysis. *Clin. Gastroenterol. Hepatol.* 2018; **16**: 1220–8.e4.
20 Whitcomb DC, Buchner AM, Forsmark CE. AGA clinical practice update on the epidemiology, evaluation, and management of exocrine pancreatic insufficiency: expert review. *Gastroenterology* 2023; **165**: 1292–301.
21 de la Iglesia D, Avci B, Kiriukova M *et al*. Pancreatic exocrine insufficiency and pancreatic enzyme replacement therapy in patients with advanced pancreatic cancer: a systematic review and meta-analysis. *United Eur. Gastroenterol. J.* 2020; **8**: 1115–25.
22 Panzuto F, Magi L, Rinzivillo M. Exocrine pancreatic insufficiency and somatostatin analogs in patients with neuroendocrine neoplasia. *Expert Opin. Drug Saf.* 2021; **20**: 383–6.
23 Ahrendt SA, McGuire GE, Pitt HA, Lillemoe KD. Why does somatostatin cause gallstones? *Am. J. Surg.* 1991; **161**: 177–83.
24 Turner H, Lindsell D, Vadivale A, Thillainayagam A, Wass J. Differing effects on gall-bladder motility of lanreotide SR and octreotide LAR for treatment of acromegaly. *Eur. J. Endocrinol.* 1999: 590–4.
25 Trendle MC, Moertel CG, Kvols LK. Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors. *Cancer* 1997; **79**: 830–4.
26 Attanasio R, Mainolfi A, Grimaldi F *et al*. Somatostatin analogs and gallstones: a retrospective survey on a large series of acromegalic patients. *J. Endocrinol. Invest.* 2008; **31**: 704–10.
27 Brighi N, Lamberti G, Maggio I *et al*. Biliary stone disease in patients receiving somatostatin analogs for neuroendocrine neoplasms. A retrospective observational study. *Dig. Liver Dis.* 2019; **51**: 689–94.
28 European Association for the Study of the Liver. EASL clinical practice guidelines on the prevention, diagnosis and treatment of gallstones. *J. Hepatol.* 2016; **65**: 146–81.
29 Brighi N, Panzuto F, Modica R *et al*. Biliary stone disease in patients with neuroendocrine tumors treated with somatostatin analogs: a multicenter study. *Oncologist* 2019; **25**: 259–65.
30 Norlén O, Hessman O, Stålberg P, Åkerström G, Hellman P. Prophylactic cholecystectomy in midgut carcinoid patients. *World J. Surg.* 2010; **34**: 1361–7.
31 Alonso-Gordoa T, Manneh R, Grande E, Molina-Cerrillo J. High-dose somatostatin analogs for the treatment of neuroendocrine neoplasms: where are we now? *Curr. Treat. Options Oncol.* 2022; **23**: 1001–13.
32 Panzuto F, Ricci C, Rinzivillo M *et al*. The antiproliferative activity of high-dose somatostatin analogs in gastro-entero-pancreatic neuroendocrine tumors: a systematic review and meta-analysis. *J. Clin. Med.* 2022; **11**: 6127.
33 Pavel M, Ćwikła JB, Lombard-Bohas C *et al*. Efficacy and safety of high-dose lanreotide autogel in patients with progressive pancreatic or midgut neuroendocrine tumours: CLARINET FORTE phase 2 study results. *Eur. J. Cancer* 2021; **157**: 403–14.
34 Strosberg J, El-Haddad G, Wolin E *et al*. Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. *N. Engl. J. Med.* 2017; **376**: 125–35.
35 Singh S, Halperin DM, Myrehaug S *et al*. [^{177}Lu]Lu-DOTA-TATE in newly diagnosed patients with advanced grade 2 and grade 3, well-differentiated gastroenteropancreatic neuroendocrine tumors: Primary analysis of the phase 3 randomized NETTER-2 study. *J Clin Oncol* 2024; **42**: abstr LBA588. https://doi.org/10.1200/JCO.2024.42.3_suppl.LBA588.
36 Lamberti G, Faggiano A, Brighi N *et al*. Nonconventional doses of somatostatin analogs in patients with progressing well-differentiated neuroendocrine tumor. *J. Clin. Endocrinol. Metabol.* 2019; **105**: 194–200.
37 Laing E, Gough K, Krishnasamy M, Michael M, Kiss N. Prevalence of malnutrition and nutrition-related complications in patients with gastroenteropancreatic neuroendocrine tumours. *J. Neuroendocrinol.* 2022; **34**: e13116.

38 Maasberg S, Knappe-Drzikova B, Vonderbeck D *et al*. Malnutrition predicts clinical outcome in patients with neuroendocrine neoplasia. *Neuroendocrinology* 2017; **104**: 11–25.
39 Herrera-Martínez Y, Alzas Teomiro C, León Idougourram S *et al*. Sarcopenia and ghrelin system in the clinical outcome and prognosis of gastroenteropancreatic neuroendocrine neoplasms. *Cancer* 2022; **14**: 111.
40 Sebastian-Valles F, Sánchez de la Blanca Carrero N, Rodríguez-Laval V *et al*. Impact of change in body composition during follow-up on the survival of GEP-NET. *Cancer* 2022; **14**: 5189.
41 Yadegarfar G, Friend L, Jones L *et al*. Validation of the EORTC QLQ-GINET21 questionnaire for assessing quality of life of patients with gastrointestinal neuroendocrine tumours. *Br. J. Cancer* 2013; **108**: 301–10.
42 Gosain R, Gupta M, Roy AM, Strosberg J, Glaser KM, Iyer R. Health-related quality of life (HRQoL) in neuroendocrine tumors: a systematic review. *Cancer* 2022; **14**: 1428.
43 Rinke A, Neary MP, Eriksson J, Hunger M, Doan T, Karli D, Arnold R. Health-related quality of life for long-acting octreotide versus placebo in patients with metastatic midgut neuroendocrine tumors in the Phase 3 PROMID trial. *Neuroendocrinology* 2019; **109**: 141–51.
44 Sorbye H, Meyer LS, Mordal KE, Myhre S, Thiis-Evensen E. Patient reported symptoms, coping and quality of life during somatostatin analogue treatment for metastatic small-intestinal neuroendocrine tumours. *Health Qual. Life Outcomes* 2020; **18**: 188.
45 Adams JR, Ray D, Willmon R, Pulgar S, Dasari A. Living with neuroendocrine tumors: assessment of quality of life through a mobile application. *JCO Clin. Cancer Inform.* 2019; **3**: 1–10.
46 La Salvia A, Modica R, Rossi RE *et al*. Targeting neuroendocrine tumors with octreotide and lanreotide: key points for clinical practice from NET specialists. *Cancer Treat. Rev.* 2023; **117**: 102560.