Long-Acting Somatostatin Analogue Safety Monitoring Protocol for Outpatients With Neuroendocrine Tumors

JORDAN GABRIELSEN,[1] PharmD, GIANNA GIRONE,[1] PharmD, BONITA BENNETT,[2] BSN, RN, and ANNA JUNG,[2] PharmD, BCPS

From [1]Thomas Jefferson University, Philadelphia, Pennsylvania; [2]Hospital of the University of Pennsylvania, Perelman Center for Advanced Medicine, Philadelphia, Pennsylvania

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Anna Jung, PharmD, BCPS, Penn Medicine, University of Pennsylvania Health System, 3400 Civic Center Boulevard, Philadelphia, PA 19104.
E-mail: anna.jung@uphs.upenn.edu

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Abstract

Somatostatin analogues (SSAs) are widely used in the long-term treatment of neuroendocrine tumors (NETs) and have a relatively favorable safety profile. However, SSAs are associated with specific side effects that are important to monitor. Currently, there is no standardized safety monitoring protocol for health-care professionals to use as a reference when initiating patients on long-acting SSAs. With the expansion of SSA use from symptomatic control to include antiproliferative tumor treatment in patients with NETs, it is increasingly important that patients taking these medications are properly monitored. The purpose of this analysis was to develop a comprehensive, practical SSA safety monitoring protocol for patients with NETs in the outpatient setting. This strategy was based on side effect frequencies that were reported and the monitoring parameters used in influential clinical and safety trials. Based on our assessment, we consider monitoring gallbladder imaging, laboratory tests (including blood chemistry, thyroid-stimulating hormone, hemoglobin A1c, and stool studies), vital signs, and physical examinations as the most important parameters when evaluating the safety of long-term SSA therapy. Due to the frequency at which patients experienced diarrhea as a side effect in clinical trials, questions about urgency, frequency, timing, consistency, odor, and color of bowel movements should be asked as part of the follow-up visits every 6 months to help differentiate between drug-induced vs. disease-associated causes. This broad monitoring strategy for patients receiving long-term SSAs was developed specifically for patients with NETs; however, the use of this protocol could be expanded to other indications in the future.

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Long-acting formulations of somatostatin analogues (SSAs) that are approved for use include octreotide (Sandostatin LAR Depot, Novartis Pharmaceuticals Corporation, 2019a; Sandostatin LAR, Novartis Pharmaceuticals UK Ltd, 2018a), lanreotide (Somatuline Depot, Ipsen Biopharmaceuticals, Inc, 2019; Somatuline Autogel, Ipsen Ltd, 2019), and pasireotide (Signifor LAR, Novartis Pharmaceuticals Corporation, 2019c; Signifor powder and solvent for suspension for injection, Novartis Pharmaceuticals UK Ltd, 2018c). The approved indications for each SSA differ—all SSAs are approved for use in acromegaly; however, only long-acting octreotide and lanreotide are approved for use in the treatment of neuroendocrine tumors (NETs). Globally, all formulations of long-acting octreotide and lanreotide are approved for functional symptoms associated with NETs (e.g., carcinoid syndrome); in some geographic regions, long-acting octreotide and lanreotide are also approved for the antiproliferative treatment of advanced NETs. Other indications vary based on the individual SSA and also by geographic region (see Appendix A); these include thyrotrophic adenomas, diarrhea associated with vasoactive intestinal peptide-secreting tumors, and Cushing disease. Octreotide is also used off label under some circumstances to control gastrointestinal bleeding (Nardone, Compare, Martino, & Rocco, 2018).

Like native somatostatins, SSAs inhibit endocrine peptides and hormones produced excessively in both NETs and acromegaly (Ipsen Biopharmaceuticals, Inc., 2019; Novartis Pharmaceuticals Corporation, 2019a). Somatostatin analogues are known to affect the production of human growth hormone, serotonin, thyroid-stimulating hormone (TSH), gastrin, insulin, and glucagon (Novartis Pharmaceuticals Corporation, 2019a). These medications were initially used to palliate hormonal symptoms associated with carcinoid syndrome seen in many patients with advanced NETs. However, the therapeutic role of these agents has expanded significantly in recent years, mostly due to research indicating that SSAs also slow tumor progression in patients with NETs (Caplin et al., 2014; Rinke et al., 2009). A phase III clinical trial of 85 patients demonstrated that long-acting octreotide prolonged the median time to tumor progression in patients with metastatic midgut NETs compared with those receiving placebo: 14.3 vs. 6 months, respectively (hazard ratio [HR], 0.34; p = .000072; Rinke et al., 2009). For advanced gastroenteropancreatic NETs, a phase III clinical trial of 204 patients demonstrated that long-acting lanreotide increased the progression-free survival compared with placebo: not reached vs. 18 months (HR, 0.47; $p < .001$; Caplin et al., 2014).

Long-acting SSAs octreotide and lanreotide are currently recommended by international guidelines as the first-line treatment for carcinoid syndrome symptoms and tumor control in advanced gastrointestinal and lung NETs (Caplin et al., 2015; Pavel et al., 2016; Strosberg et al., 2017). Given the relatively indolent clinical course of most NETs (Dasari et al., 2017), SSAs are often used for extended periods of time. A recent survey of patients with carcinoid syndrome symptoms reported a mean (± standard deviation) duration of SSA use of 6.1 ± 4.7 years (Halperin et al., 2017). In cases of disease progression or refractory carcinoid syndrome while receiving a standard dose of SSA, dose escalation above the upper labeled dosages is an option to improve efficacy (Chan et al., 2017; Pavel et al., 2016) and SSAs may be combined with locoregional therapies or targeted drugs, such as everolimus, for tumor control in patients with functionally active NETs (Pavel et al., 2016). Somatostatin analogues may also be used in combination with the recently approved telotristat ethyl for control of refractory carcinoid syndrome diarrhea in adults who are not adequately controlled on SSA therapy alone, or with ^{177}Lu-Dotatate peptide receptor radionuclide therapy for tumor control (Advanced Accelerator Applications, 2018; Lexicon Pharmaceuticals, Inc., 2017). Based on our clinical experience, SSAs are also used in combination with cytotoxic chemotherapy regimens, such as capecitabine and temozolomide (Kunz et al., 2018), as determined by multidisciplinary team (MDT) discussion (Metz et al., 2012). This chronic use of SSAs, use above upper labeled dosages, and combination with other treatments underscore the importance of adverse event monitoring and management to ensure the maintenance of patient quality of life (Singh et al., 2017).

Somatostatin analogues are considered to be generally well tolerated (Pavel & De Herder,

2017), with a lack of serious adverse events (Pavel et al., 2016) and low rates of discontinuation due to treatment-related adverse events in phase III clinical trials (Caplin et al., 2014; Pavel et al., 2011; Rinke et al., 2009). However, side effects may occur due to the ubiquitous inhibition of endocrine hormones. The most common adverse events include abdominal discomfort, nausea, diarrhea, steatorrhea, and injection-site pain (Modlin, Pavel, Kidd, & Gustafsson, 2010). Of note, diarrhea is also one of the main symptoms of carcinoid syndrome (Boutzios & Kaltsas, 2015), which complicates the observance of diarrhea as a side effect of SSA treatment, further supporting the need for a monitoring protocol. Less frequent side effects include cholelithiasis, dysregulation of glucose (hypoglycemia and hyperglycemia), and thyroid function abnormalities (Ipsen Biopharmaceuticals, Inc., 2019; Modlin et al., 2010; Novartis Pharmaceuticals Corporation, 2019a). Other side effects include sinus bradycardia and vitamin B_{12} deficiency (Ipsen Biopharmaceuticals, Inc., 2019; Novartis Pharmaceuticals Corporation, 2019a, 2019c).

Although the safety of SSAs has been studied in clinical trials, there are currently no published, standardized safety monitoring recommendations for health-care professionals to reference when initiating patients on these medications. With the expansion of the SSA indication in NETs from symptomatic control to include antiproliferative tumor treatment, their chronic use, use above upper labeled dosages, combination with other drugs, and the similarity of some side effects with disease symptoms, it is important that patients taking these medications are properly monitored. The purpose of this project was to develop an SSA safety monitoring protocol for patients with NETs in the outpatient setting; however, the use of this protocol could be expanded to other indications. The goal of this analysis was to develop a robust, practical safety monitoring protocol for use with patients initiating therapy with long-acting SSAs for NETs using the safety data available in published clinical trials along with the medication package inserts.

METHODS

Data Sources/Search Strategy

PubMed (1966–present) was primarily used to identify relevant clinical trial publications, along with Scopus (2004–present). The last search was performed on October 12, 2017. English language limits were applied in all databases. No publication date limits were applied. Databases were searched for the keywords: "long-acting somatostatin analogue," "octreotide," "lanreotide," "pasireotide," "acromegaly," "neuroendocrine tumor," "safety," and "side effects." Article nominations supplemented the database searching: PROMID (Rinke et al., 2009), CLARINET (Caplin et al., 2014), ACCESS (Fleseriu, Rusch, & Geer, 2017), and others (Rubin et al., 1999; Wolin et al., 2015).

Study Inclusion Criteria

Criteria used to select clinical studies included the following: long-acting SSAs used to treat patients with acromegaly or NETs; at least one study arm with patients receiving long-acting SSA monotherapy; influence of trial on clinical approval or trial designed specifically to assess efficacy and safety; robustness of preinitiation and follow-up safety monitoring procedures and reporting of side effect frequency; and average treatment duration of at least 6 months.

Data Collection From Selected Studies

Selected publications were searched for side effect monitoring parameters, including preinitiation and follow-up monitoring. Reported side effect frequency (overall number and percentage of patients with treatment-emergent and treatment-related adverse events of any grade) was tabulated. Safety analyses were searched for the percentage of patients who experienced side effects of interest (treatment-emergent or treatment-related adverse events of interest, any grade) in the study arm receiving long-acting SSA monotherapy, and the results were collected and summarized using a spreadsheet.

Generation of the Monitoring Protocol

The long-acting SSA side effect monitoring protocol was developed based on the findings of the clinical trial analysis, considering the preinitiation and follow-up safety monitoring procedures used in each study; the side effect frequency results found in the studies selected for inclusion; and the practicality of each side effect monitoring parameter in a clinical setting. Priority was given to monitoring side

effects with high frequencies or those that posed the most health risk for patients based on clinical judgement. The information regarding safety and adverse events detailed in the medication package insert was also taken into consideration, along with expert knowledge and guidance from MDTs experienced in the treatment of NETs with SSAs at the Perelman Center for Advanced Medicine, Hospital of the University of Pennsylvania.

RESULTS

Clinical Trial Selection

A total of eight clinical studies were identified and selected for analysis. Treatments examined in these studies included long-acting octreotide in NETs (Pavel et al., 2011; Rinke et al., 2009; Rubin et al., 1999), lanreotide prolonged-release (PR) in acromegaly and NETs (Chanson, Leselbaum, Blumberg, & Schaison, 2000; Ruszniewski et al., 2004), lanreotide autogel/depot in NETs (Caplin et al., 2014), and long-acting pasireotide in acromegaly and NETs (Fleseriu et al., 2017; Wolin et al., 2015).

Side Effect Frequency Analysis

Table 1 summarizes the selected studies and provides the overall frequencies of treatment-emergent and treatment-related adverse events, as available. Comparison of the frequency of individual side effects of interest experienced with SSAs in influential clinical trials is provided in Figure 1. The most common side effects of interest when assessing the individual adverse events of four studies with detailed treatment-related adverse event data (CLARINET by Caplin et al., 2014; RADIANT-2 by Pavel et al., 2011; and others by Rubin et al., 1999 and Wolin et al., 2015), were hyperglycemia (0%–28%), diarrhea (0%–26%), fatigue (0%–23%), nausea (3%–16%), abdominal pain (0%–14%), and cholelithiasis (0%–10%). Diarrhea was reported in every study analyzed except for one (Rubin et al., 1999), which reported steatorrhea in one patient and flatulence in one patient who were receiving long-acting octreotide every 4 weeks. Nausea was reported in every study assessed for adverse event frequencies. The ACCESS (Fleseriu et al., 2017) trial and phase III study of long-acting pasireotide in NETs (Wolin et al., 2015) demonstrated an increased frequency of hyperglycemia with the use of pasireotide (up to 28%) when compared with other trials using lanreotide or octreotide (up to 5%), although all three SSAs have been known to cause hyperglycemia. Fatigue was reported in every study analyzed except for one by Rubin and colleagues (1999), which did report one patient in the long-acting octreotide 10 mg every 4 weeks arm to have asthenia.

Safety Monitoring Analysis

A summary of safety monitoring in influential clinical trials is provided in Figure 2. The most common baseline monitoring procedures performed prior to SSA initiation in all the clinical trials assessed were gallbladder ultrasounds, vital sign examinations, electrocardiograms, and clinical laboratory tests (including blood chemistry, hematology, fasting and postprandial blood glucose, and thyroid function). The most common follow-up monitoring procedures performed in these clinical trials were physical examinations, vital sign examinations, clinical laboratory evaluations, gallbladder ultrasounds, and electrocardiograms. These were done at varying intervals among the trials, from 1 month, 3 months, 6 months, and up to 1 year post initiation.

Most of the trials also performed monitoring of potential adverse events "regularly." Depending on the trial, these included blood chemistry, thyroid function, hematologic tests, fasting blood glucose and post-prandial glucose, hemoglobin A1c (HbA1c), and stool studies. CLARINET (Caplin et al., 2014), ACCESS (Fleseriu et al., 2017), and other lanreotide safety trials (Chanson et al., 2000; Ruszniewski et al., 2004) performed gallbladder ultrasounds at baseline and at various intervals during their long-term monitoring of the patients, including intervals of every 3 months to yearly.

Monitoring Protocol Development

Based on the analysis, gallbladder imaging, laboratory tests (including blood chemistry, HbA1c, TSH), vital signs, and physical examinations were determined to be the most important monitoring parameters when evaluating the safety of long-term SSA therapy. These were therefore included in the monitoring protocol (Figure 3). Health-care professionals should refer to the medication package inserts regarding dose modifications as needed while observing patients with this monitoring

Table 1. Description of Clinical Studies Analyzed and Overall Frequency of Adverse Events

Trial	Disease	Treatment arms	Intent-to-treat population, n	Safety set, n	Overall frequency of TEAEs, n (%)	Overall frequency of TRAEs, n (%)
Rubin et al., 1999 Randomized trial	NETs	Short-acting octreotide q8h	26	26	(84–95.4)	6 (23)
		Long-acting octreotide 10 mg q4wk[a]	22	22	(84–95.4)	5 (23)
		Long-acting octreotide 20 mg q4wk[a]	20	20	(84–95.4)	6 (30)
		Long-acting octreotide 30 mg q4wk[a]	25	25	(84–95.4)	5 (20)
PROMID (Rinke et al., 2009) Phase III	NETs	Long-acting octreotide 30 mg q28d[a]	42	Not specified		
		Placebo q28d	43	Not specified		
RADIANT-2 (Pavel et al., 2011) Phase III	NETs	Everolimus 10 mg qd + long-acting octreotide 30 mg q28d	216	215	Not specified	
		Placebo + long-acting octreotide 30 mg q28d[a]	213	211	Not specified	
Chanson et al., 2000 12-month multicenter	Acromegaly	Lanreotide PR 30 mg q14d[a]	116	58	58 (100)	Not specified
Ruszniewski et al., 2004 Phase II/III dose titration	NETs	Lanreotide PR 90 mg q28 for first 2 injections, then titrated according to response (60 mg or 120 mg q28d) for subsequent injections[a]	75	71	Not specified	26 (37)
CLARINET (Caplin et al., 2014) Phase III	NETs	Lanreotide autogel 120 mg q28d[a]	101	101	89 (88)	50 (50)
		Placebo q28d	103	103	93 (90)	29 (28)
ACCESS (Fleseriu et al., 2017) Expanded treatment protocol	Acromegaly	Long-acting pasireotide 40 mg q28d[a]	44	44	Not specified	
Wolin et al., 2015 Phase III	NETs	Long-acting pasireotide 60 mg q28d[a]	53	53	Not specified	

Note. NETs = neuroendocrine tumors; PR = prolonged release; qd = every day; q14d = every 14 days; q28d = every 28 days; q4wk = every 4 weeks; TEAEs = treatment-emergent adverse events; TRAEs = treatment-related adverse events.
[a]Treatment arm of interest for analysis of adverse events.

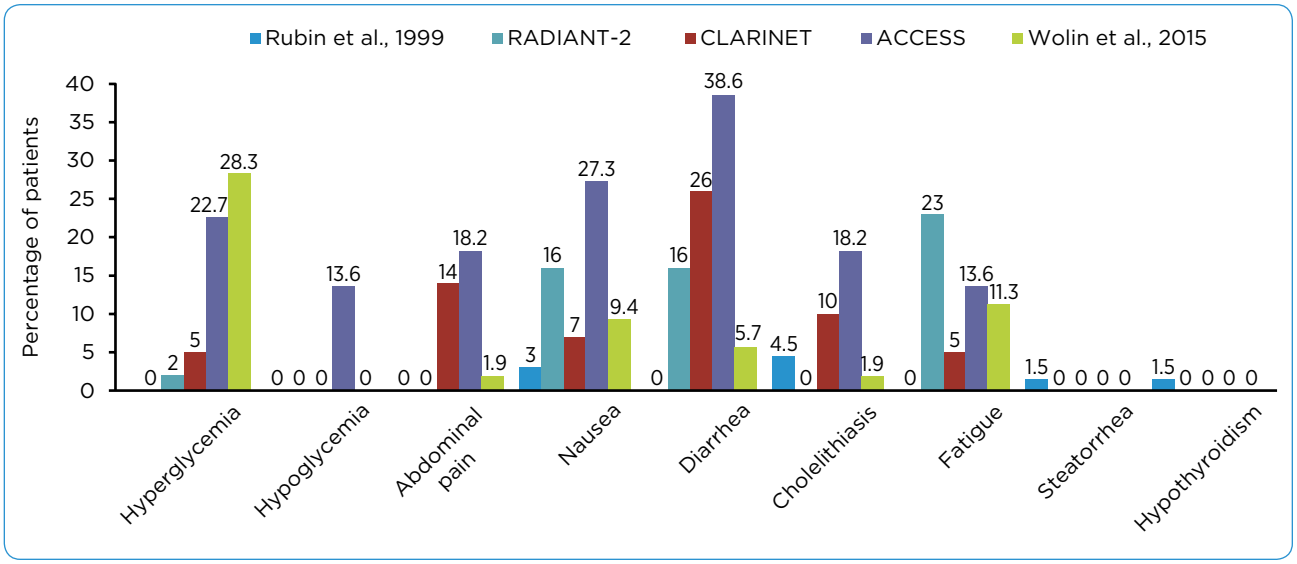

Figure 1. Frequency of adverse events of interest in influential clinical studies of somatostatin analogues. Based on reported data from clinical studies: Rubin et al., 1999, treatment-related adverse events reported in any patient (pooled data for long-acting octreotide); RADIANT-2, treatment-related adverse events in at least 10% of patients in one treatment arm; CLARINET, treatment-related adverse events in at least 5% of patients in one treatment arm; ACCESS, adverse events in at least 7% of patients; Wolin et al, 2015, treatment-related adverse events reported in at least 5% of patients in one treatment arm. Data from PROMID (Rinke et al., 2009) are not included because these details of adverse events were not reported from this study.

protocol. Based on the monitoring frequency and the average frequency of cholethiasis reported in these clinical trials, we recommend that a baseline gallbladder ultrasound be performed and repeated every 6 months (unless other imaging that adequately visualizes the gallbladder is obtained). However, the interval of testing for cholethiasis may be extended in patients who do not report signs or symptoms suspicious for cholethiasis after the first year of therapy or who do not have a history of cholethiasis. Gallbladder status can also be monitored with CT and MRI performed at routine intervals during the regular care of patients with NETs.

We recommend that a complete metabolic panel and HbA1c test be performed at baseline and then repeated every 6 months. If an abnormal HbA1c value occurs, then this frequency should be increased to every 3 months, as per the 2018 American Diabetes Association standard of medical care recommendations (American Diabetes Association, 2018). Additionally, a complete blood count, TSH, vitamin B_{12}, and zinc level (for patients with excessive fluid losses maintained on total parenteral nutrition) should be ordered at baseline. Thyroid-stimulating hormone should be followed every 6 months with regular tests regardless of the level. Although SSAs are known to cause low levels of vitamin B_{12} and zinc, these side effects were not reported in any of the trials we examined. We believe that the continued monitoring of vitamin B_{12} and zinc at an interval of every 3 to 6 months is necessary in cases where a low level is detected, but otherwise should be monitored in the future only if there is an indication and at the clinician's discretion. Monitoring of vitamin B_{12}, zinc, and other vitamins may be necessary following bowel surgery.

Lastly, to ensure a complete understanding of the patient's health status, we also recommend that vital signs, a physical examination, and a thorough medical history, including the history of current medications and specific inquiry about history of cardiovascular disease, diabetes mellitus, and gastrointestinal disorders, be taken at baseline and repeated every 6 months. Due to the frequency at which patients experienced diarrhea as a side effect, questions about urgency, frequency, timing (i.e., nocturnal, or in relation to receipt of SSA injection), consistency, odor (i.e., malodorous), and color of bowel movements should be asked as part of the follow-up visits every 6 months. Patients

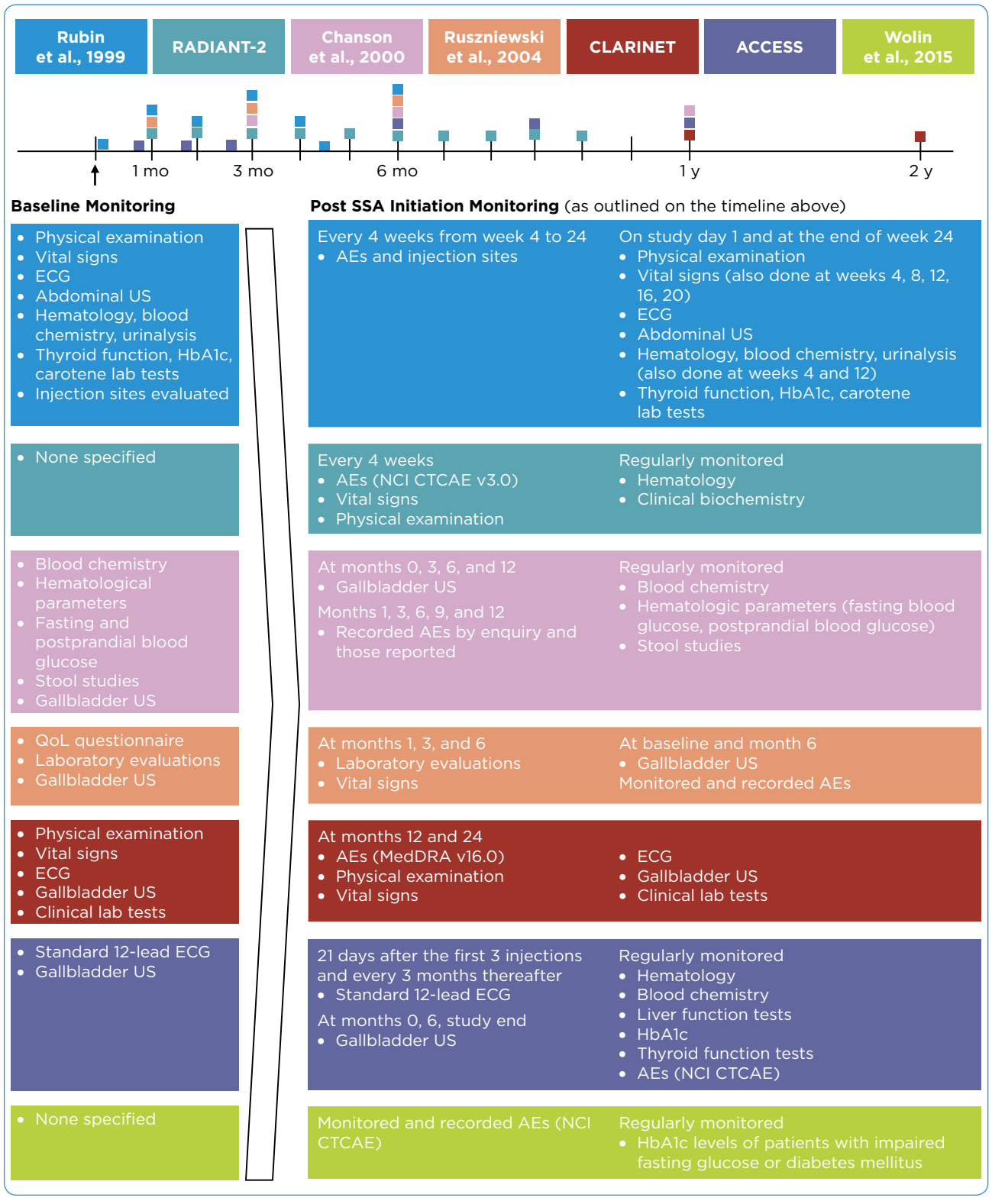

Figure 2. Timeline of safety monitoring in influential clinical trials with somatostatin analogues.
AE = adverse events; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiography; HbA1c = hemoglobin A1c; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; QoL = quality of life; SSA = somatostatin analogues; US = ultrasound; v = version.

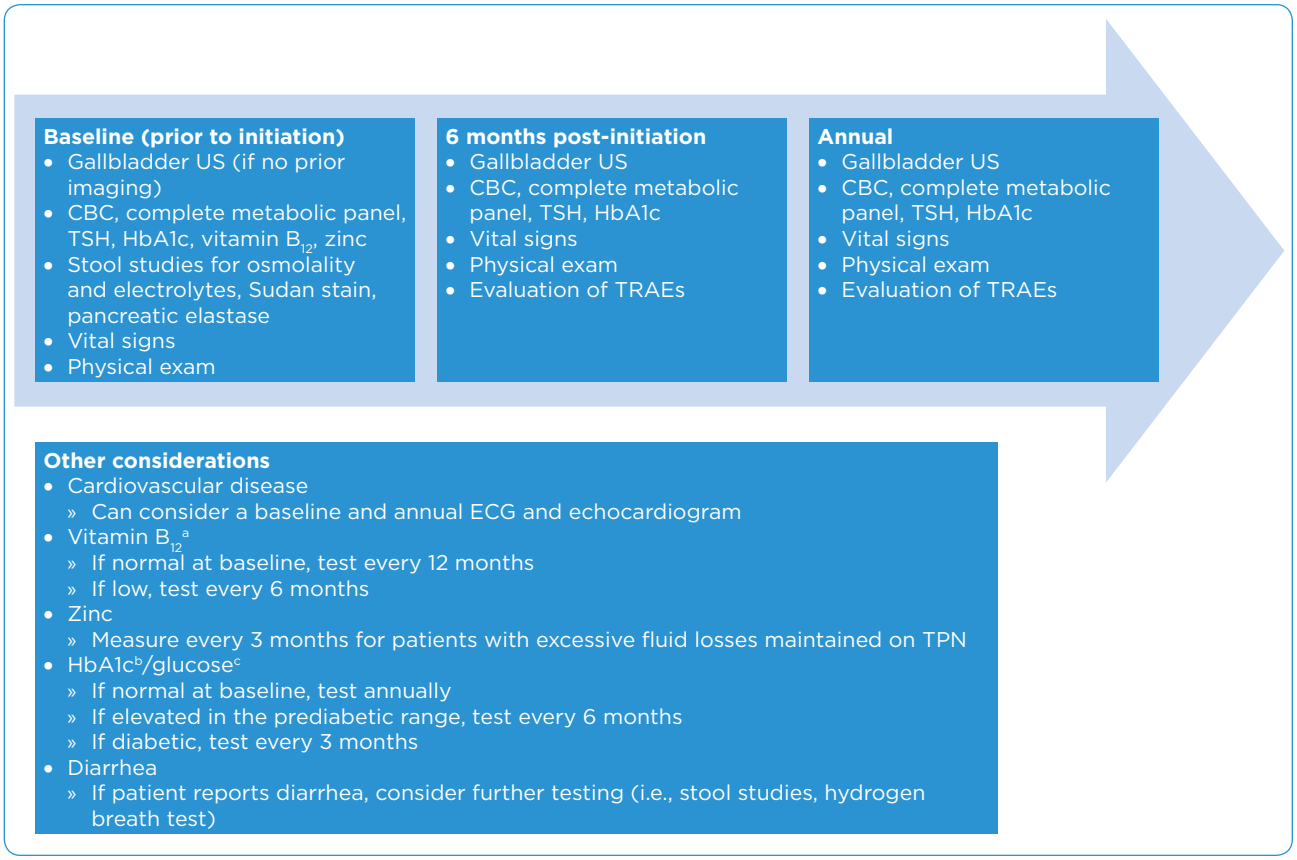

Figure 3. Proposed protocol for monitoring patients with neuroendocrine tumors receiving long-term treatment with somatostatin analogues. CBC = complete blood count; ECG = electrocardiogram; TPN = total parenteral nutrition; TRAEs = treatment-related adverse events; TSH = thyroid-stimulating hormone; US = ultrasound.
[a]Vitamin B_{12} normal reference values: 211–946 pg/mL.
[b]HbA1c normal reference values: 4.0%–5.6%. Prediabetic HbA1c: 5.7%–6.4%. Diabetic HbA1c: ≥ 6.5%.
[c]Fasting plasma glucose (FPG) normal reference values: 70–99 mg/dL. Prediabetic FPG: 100–125 mg/dL. Diabetic FPG: > 126 mg/dL.

commonly experience steatorrhea with this medication, owing to a reduction in pancreatic enzyme production leading to malabsorption. Stool studies for fat, elastase, osmolality, and electrolytes and a hydrogen breath test may also be helpful in determining etiology (Loser, Mollgaard, & Folsch, 1996). Additionally, a baseline and annual electrocardiogram in patients with known cardiovascular disease is reasonable because of the known risk of bradycardia with these medications.

DISCUSSION

Long-acting SSAs octreotide and lanreotide are currently recommended as the first-line treatment for carcinoid syndrome symptoms and tumor control in advanced gastrointestinal and lung NETs (Caplin et al., 2015; Pavel et al., 2016; Strosberg et al., 2017). Using safety data available from influential trials of long-acting SSAs, we have formulated a generalized safety monitoring strategy that can be used for the long-term monitoring of patients receiving long-acting SSA treatment for NETs. This strategy is based on the side effect frequencies that were reported and the monitoring parameters used in clinical and safety trials, along with expert knowledge and guidance from MDTs experienced in treating NETs with SSAs at the Perelman Center for Advanced Medicine at the Hospital of the University of Pennsylvania.

The prevalence of NETs is rising and in the United States is now more common than the

prevalence of esophageal cancer, gastric cancer, or pancreatic cancer (Yao et al., 2008). The creation of a standardized long-acting SSA safety monitoring protocol will enable caregivers to ensure comprehensive monitoring of patients with NETs who are started on these medications, document safety events in a standardized manner, compare their findings to historical safety data, and identify potential improvements in safety monitoring, side effect prevention, and overall patient care. It also serves to educate other caregivers who may interact with medical records and may be unfamiliar with the treatment of these rare tumors, the medications used, and their potential side effects.

In addition, patients may have a pharmacy consult for medication therapy management, and it is therefore important that pharmacists are knowledgeable about side effects that could be caused by SSAs. An MDT approach should be implemented for the long-term care of oncology patients, including those with NETs (Metz et al., 2012). Adding a pharmacist to the MDT could be a valuable opportunity for patients to have additional education and care, including the provision of recommendations for managing and reporting adverse events. Pharmacists may promote medication compliance, consistency in dosing regimen, and prevention of gaps in medication availability, thus enhancing patient outcomes and patient satisfaction.

Limitations of this analysis include the heterogeneity of the trials identified in the search, which varied in design, patient population, and reporting of adverse events. Few trials reported detailed treatment-related adverse event data, most were short-term trials, and there were no head-to-head trials of SSAs at approved dosages. This monitoring protocol should be optimized through use and provision of feedback. Patient-specific factors should also play a role in the use of the protocol. Some patients may not need zinc level tests or electrocardiography if there is no known cardiovascular disease.

Monitoring of patients' safety during SSA treatment for NETs is an important component of patient management, particularly due to the widespread and chronic use of SSAs for this disease, and the similarity between disease symptoms and side effects associated with SSA use. Although the safety of SSAs has been assessed in several clinical trials, there are currently no published, standardized safety monitoring recommendations for health-care professionals to reference when initiating these medications for their patients. We developed a thorough, practical safety monitoring protocol for use with patients initiating therapy with long-acting SSAs for NETs. This broad strategy was developed specifically for patients with NETs; however, the use of this protocol could be expanded to other indications in the future. Active monitoring and prompt identification of side effects can ensure long-term patient safety.

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Disclosure

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Appendix A. Supplementary Table: Information on Somatostatin Analogue Formulations

SSA formulations	Region	Marketed name	Standard administration frequency[a]	Standard administration route[a]	Indications[a]
Octreotide					
Short-acting octreotide	US	Sandostatin (Novartis Pharmaceuticals Corporation, 2019d)	2–3 times daily	Subcutaneous	Acromegaly • Patients with acromegaly who have had an inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses Carcinoid syndrome • Symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease VIPomas • Profuse watery diarrhea associated with VIP-secreting tumors (VIPomas)
	EU	Sandostatin (Novartis Pharmaceuticals UK Ltd, 2019)	Daily with frequency varying by indication	Subcutaneous	Acromegaly • Acromegaly, a condition where the body produces too much growth hormone Functional GI NET symptoms • Relieve symptoms associated with some tumors of the GI tract (e.g., carcinoid tumors, VIPomas, glucagonomas, gastrinomas, insulinomas) TSH-secreting pituitary tumors • Pituitary tumors that produce too much TSH, when other types of treatment (surgery or radiotherapy) are not suitable or have not worked; after radiotherapy to cover the interim period until the radiotherapy becomes fully effective Prevention of complications • To prevent complications following surgery of the pancreas gland • To stop bleeding and to protect from rebleeding from ruptured gastroesophageal varices in cirrhotic patients
Long-acting octreotide	US	Sandostatin LAR Depot (Novartis Pharmaceuticals Corporation, 2019a)	Every 4 weeks	Intramuscular	Acromegaly • Long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy Carcinoid syndrome • Long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors VIPomas • Long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors (VIPomas)

Note. GEP = gastroenteropancreatic; GI = gastrointestinal; IGF-1 = insulin-like growth factor; NETs = neuroendocrine tumors; PFS = progression-free survival; SSA = somatostatin analogue; TSH = thyroid-stimulating hormone; VIP = vasoactive intestinal peptide.
[a]The most up-to-date prescribing information or summary of product characteristics should be accessed from the manufacturer's website for a current list of indications and dosing/administration.

Continued on following page

Appendix A. Supplementary Table: Information on Somatostatin Analogue Formulations (cont.)

SSA formulations	Region	Marketed name	Standard administration frequency[a]	Standard administration route[a]	Indications[a]
Long-acting octreotide (cont.)	EU	Sandostatin LAR (Novartis Pharmaceuticals UK Ltd, 2018a)	Every 4 weeks	Intramuscular	Acromegaly • Acromegalic patients in whom surgery is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective Functional GEP NET symptoms • Symptoms associated with functional GEP NETs (eg, carcinoid tumors with features of carcinoid syndrome) Advanced midgut NETs • Advanced NETs of midgut or unknown primary origin where non-midgut sites of origin have been excluded TSH-secreting pituitary adenomas • TSH-secreting pituitary adenomas when secretion has not normalized after surgery and/or radiotherapy; in patients in whom surgery is inappropriate; in irradiated patients until radiotherapy is effective
Lanreotide					
Lanreotide prolonged-release	EU	Somatuline LA (Ipsen Ltd, 2018)	Every 14 days	Intramuscular	Acromegaly • Acromegaly when the circulating levels of growth hormone and/or IGF-1 remain abnormal after surgery and/or radiotherapy Thyrotropic adenomas • Thyrotropic adenomas when the circulating level of TSH remains inappropriately high after surgery and/or radiotherapy Functional NET symptoms • Relief of symptoms associated with NETs (particularly carcinoid)
Lanreotide long-acting release	US	Somatuline Depot (Ispen Biopharmaceuticals, Inc., 2019)	Every 4 weeks	Deep subcutaneous	Acromegaly • Long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy Advanced GEP NETs • Adults with unresectable, well- or moderately differentiated, locally advanced, or metastatic GEP NETs to improve PFS Carcinoid syndrome • Adults with carcinoid syndrome; when used, it reduces the frequency of short-acting SSA rescue therapy

Note. GEP = gastroenteropancreatic; GI = gastrointestinal; IGF-1 = insulin-like growth factor; NETs = neuroendocrine tumors; PFS = progression-free survival; SSA = somatostatin analogue; TSH = thyroid-stimulating hormone; VIP = vasoactive intestinal peptide.
[a]The most up-to-date prescribing information or summary of product characteristics should be accessed from the manufacturer's website for a current list of indications and dosing/administration.

Appendix A. Supplementary Table: Information on Somatostatin Analogue Formulations (cont.)

SSA formulations	Region	Marketed name	Standard administration frequency[a]	Standard administration route[a]	Indications[a]
Lanreotide long-acting release (cont.)	EU	Somatuline Autogel (Ipsen Ltd, 2019)	Every 28 days	Deep subcutaneous	Acromegaly • Acromegaly when the circulating levels of growth hormone and/or IGF-1 remain abnormal after surgery and/or radiotherapy, or in patients who otherwise require medical treatment Advanced GEP NETs • Adults with unresectable, locally advanced, or metastatic G1 and a subset of G2 (Ki-67 index up to 10%) GEP NET Functional NET symptoms • Treatment of symptoms associated with NETs (particularly carcinoid)
Pasireotide					
Short-acting pasireotide	US	Signifor (Novartis Pharmaceuticals Corporation, 2019b)	Twice daily	Subcutaneous	Cushing disease • Adult patients with Cushing disease for whom pituitary surgery is not an option or has not been curative
	EU	Signifor solution for injection (Novartis Pharmaceuticals UK Ltd, 2018b)	Twice daily	Subcutaneous	Cushing disease • Adult patients with Cushing disease for whom surgery is not an option or for whom surgery has failed
Long-acting pasireotide	US	Signifor LAR (Novartis Pharmaceuticals Corporation, 2019c)	Every 4 weeks	Intramuscular	Acromegaly • Patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option
	EU	Signifor powder and solvent for suspension for injection (Novartis Pharmaceuticals UK Ltd, 2018c)	Every 4 weeks	Intramuscular	Acromegaly • Patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another SSA Cushing disease • Adult patients with Cushing disease for whom surgery is not an option or for whom surgery has failed

Note. GEP = gastroenteropancreatic; GI = gastrointestinal; IGF-1 = insulin-like growth factor; NETs = neuroendocrine tumors; PFS = progression-free survival; SSA = somatostatin analogue; TSH = thyroid-stimulating hormone; VIP = vasoactive intestinal peptide.
[a]The most up-to-date prescribing information or summary of product characteristics should be accessed from the manufacturer's website for a current list of indications and dosing/administration.