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

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ABSTRACT

Purpose: To develop a safety monitoring protocol of somatostatin analogs in the outpatient setting.

Although the safety of somatostatin analogs has been studied in clinical trials, there are currently no published, standardized safety monitoring recommendations for healthcare professionals to reference when initiating patients on these medications. Our goal was to develop a thorough, and practical safety monitoring protocol for patients who are started on the long-acting somatostatin analog formulations using safety data available in published clinical trials.

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).

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 (M. E. 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).

RESULTS

Side Effect Frequency Analysis

The most common side effects of interest, when assessing the individual adverse events of four studies with detailed treatment-related adverse event data (CLARINET (Caplin et al., 2014), RADIANT-2 (M. E. Pavel et al., 2011), and others (Rubin et al., 1999; Wolin et al., 2015)), were hyperglycemia (0-28%), diarrhea (range 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 1 patient and flatulence in 1 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 3 study of long-acting pasireotide in NET (Wolin et al., 2015) demonstrated an increased frequency of hyperglycemia with use of pasireotide (up to 28%) when compared to 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 Rubin et al, 1999, which did report 1 patient in the long-acting octreotide 10 mg every 4 weeks arm to have asthenia (Rubin et al., 1999).

Safety Monitoring Analysis

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, Med 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, hematological 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.

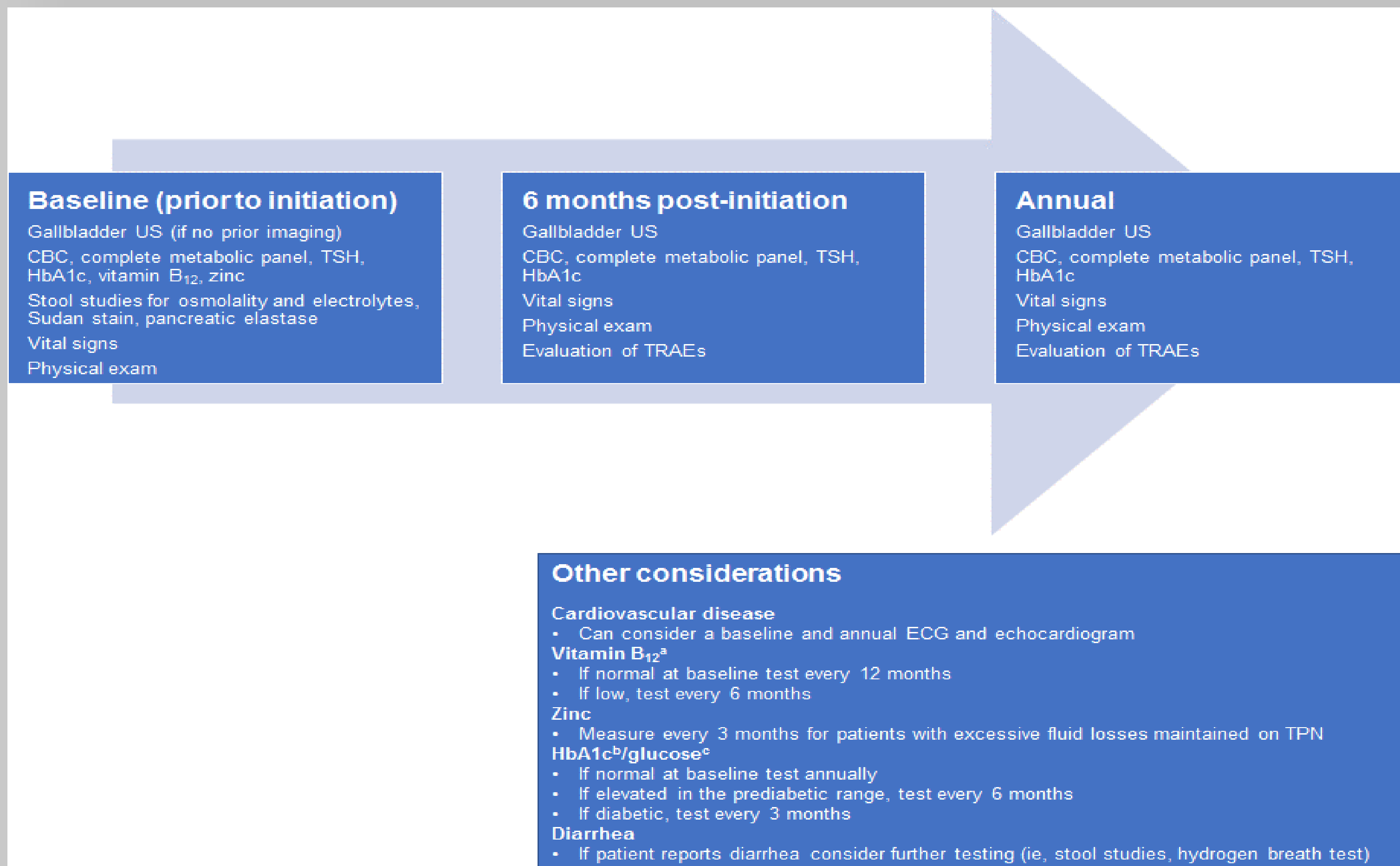# Long-Acting Somatostatin Analogue Safety Monitoring Protocol for Outpatients with Neuroendocrine Tumors

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RESULTS CONTINUED

Monitoring Protocol

Baseline (prior to initiation)
Gallbladder US (if no prior imaging)
CBC, complete metabolic panel, TSH, HbA1c, vitamin B$_{12}$, zinc
Stool studies for osmolality and electrolytes, Sudan stain, pancreatic elastase
Vital signs
Physical exam

6 months post-initiation
Gallbladder US
CBC, complete metabolic panel, TSH, HbA1c
Vital signs
Physical exam
Evaluation of TRAEs

Annual
Gallbladder US
CBC, complete metabolic panel, TSH, HbA1c
Vital signs
Physical exam
Evaluation of TRAEs

Other considerations

Cardiovascular disease
- Can consider a baseline and annual ECG and echocardiogram

Vitamin B$_{12}$[a]
- If normal at baseline test every 12 months
- If low, test every 6 months

Zinc
- Measure every 3 months for patients with excessive fluid losses maintained on TPN

HbA1c[b]/glucose[c]
- If normal at baseline test annually
- If elevated in the prediabetic range, test every 6 months
- If diabetic, test every 3 months

Diarrhea
- If patient reports diarrhea consider further testing (ie, stool studies, hydrogen breath test)

CONCLUSIONS

Using somatostatin analog safety data available from influential trials, we have formulated a generalized safety monitoring strategy that can be used for long-term monitoring of long-acting somatostatin analog formulations.

This is a broad strategy that can be applied regardless of the indication for which the somatostatin analogs are being used. The creation of a standardized long-acting somatostatin safety monitoring protocol, will enable physicians to ensure thorough monitoring of the patients they start 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.

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REFERENCES

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