Chronic use of Long-acting Somatostatin Analogues (SSAs) and Exocrine Pancreatic Insufficiency (EPI) in patients with Gastroenteropancreatic neuroendocrine tumors (GEP-NETs): An Under-recognized Adverse Effect

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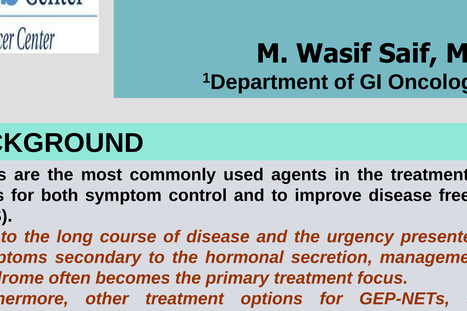
BACKGROUND

- SSAs are the most commonly used agents in the treatment of GEP-NETs for both symptom control and to improve disease free survival (DFS).
- *Due to the long course of disease and the urgency presented by the symptoms secondary to the hormonal secretion, management of the syndrome often becomes the primary treatment focus.*
- *Furthermore, other treatment options for GEP-NETs, such as chemotherapy and targeted agents may not necessarily translate into improvements in syndrome control.*
- *There are many over-the-counter medications available to individuals experiencing chronic diarrhea. However, the mechanism by which these agents act does not address the mechanisms underlying the diarrhea induced in carcinoid syndrome.*
- *Though SSAs are effective in reducing the frequency of bowel movements and episodes of flushing, but we're often forced to increase SSA dose and frequency well above label or use supplemental short-acting doses to help maintain control.*
- *Further, many patients develop tachyphylaxis.*
- *Despite all these efforts, many patients do not experience improved syndrome control.*
- The most commonly reported adverse events include injection-site discomfort and erythema, gastrointestinal (GI) disturbances such as diarrhea, abdominal pain, nausea and vomiting, biliary sludge or gallstones, and abnormal glucose metabolism.
- As these agents mimic Somatostatin, they can inhibit pancreatic hormones, leading to pancreatic insufficiency.
- EPI is misdiagnosed leading to increasing SSAs dosage, use of short acting or additional medications that not only burden the quality of life of these patients or cause additional adverse events but also add to cost of treatment.
- This common but under-published condition is easy to diagnose and treat.

Figure 1: Effect of SAAs on EPI



OBJECTIVES

Primary Objectives

- To identify incidence of EPI in pts. receiving SSAs for GEP-NETs
- To evaluate the benefit of pancreatic enzyme replacement (PER) in these pts

Secondary Objectives

- To determine the clinical and laboratory manifestations in patients receiving SSAs for GEP-NETs
- To compare the financial impact of using PER versus. intensification of the syndrome treatment.

PATIENTS & METHODS

- Retrospective chart and pharmacy review of patients with histologically confirmed GEP-NETs (6/2009 - 6/2017) was performed.
- Data collected included demographics, symptoms including diarrhea, weight loss, flatulence, etc., dose/duration of long and short-acting SSAs, use of antidiarrheal medications including OTC, use of PER, use of proton pump inhibitors (PPI) or H-2 blockers, and laboratory data, particularly tumor related markers chromogranin-A (CgA), urine 5-HIAA, along with radiological imaging (CT scan, MRI, Octreotide scan).
- Diarrhea was defined as > 2 stools/d in addition to chronic baseline diarrhea while on SAs and weight loss > 10% of baseline despite adequate caloric intake. Steatorrhea was suspected when the patient has large, "greasy", and foul-smelling stools.
- Currently the gold standard test to diagnose steatorrhea remains the 72 hour fat balance method (normal output is <7 g of fat per 24-hour period).
- Regarding EPI, records were searched for any consults made with the nutritionist or a gastroenterologist or both, and laboratory results if available on quantitative fecal fat, blood levels of fat soluble vitamins, such as Vitamins A, D, E, K and elements including Magnesium, Potassium, Zinc, Chromium, Selenium, Iron, and Iodine.
- EPI was graded according to the Pancreas exocrine enzyme

Table 1: Grades of Pancreas exocrine enzyme deficiency per (CTCAE) 4.0

Grade	1	2	3	4	5
	-	Increase in stool frequency, bulk or odor, steatorrhea	Sequelae of absorption deficiency (e.g. weight loss)	Life-threatening consequences	Death

RESULTS

- 110 pts. (age 29-87) with GEP-NETs were identified. Study schema and demographic features are shown listed in Figure 2 and Table 1.
- Based on the previous data including perfusion studies, PER was dosed to administer 25000 to 50000 USP units of lipase per meal to achieve normal fat digestion and absorption.

Figure 2: Study Schema

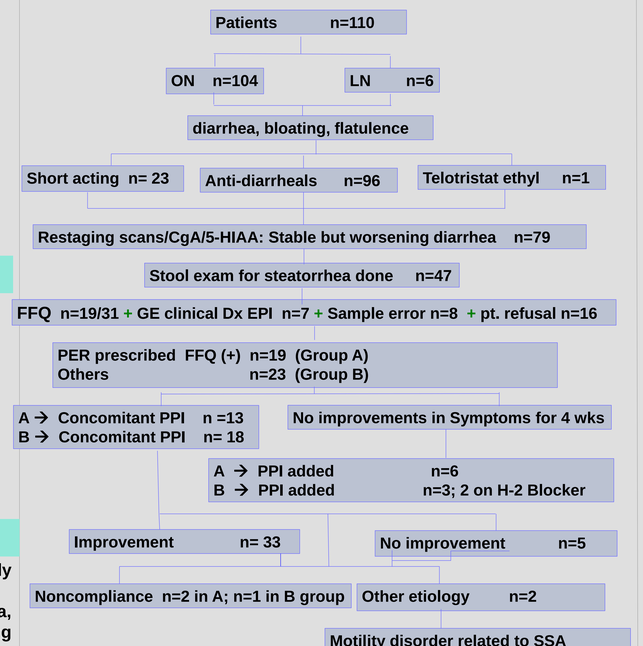


Table 1: Table 1 Patient Demographics

Total N o. of Patients	110
Median Age (range)	61 (29 – 85)
Male: Female	41:69
Ethnicity	W: 75, AA: 7, HS. 11, AS. 5, UK: 12
Site of Primary Tumor	Small Bowel: 68, Unknown: 16, Pancreas: 11, Gastric: 7, Rectal: 5, Colon: 3
Stage at diagnosis	III (17)/ IV (59)/ UK (34)

Figure 3: Grades of PEI at DX

Incidence of EPI: 38%

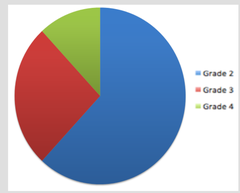


Table 2: Duration of SAAs till PEI

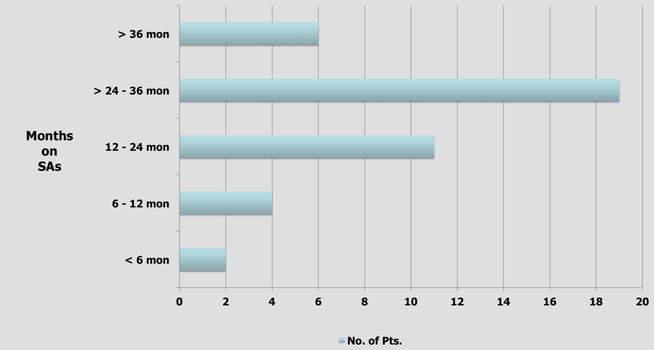
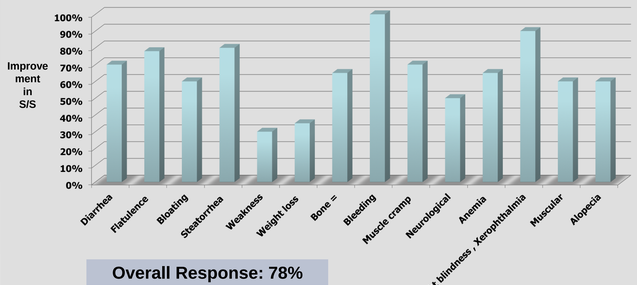


Table 3: Incidence of Vitamins & Minerals/elements Deficiency

Vit./Min. Deficiency	N 11/42 (26 %)
A	2 (18%)
D	7 (64%)
E	2 (18%)
K	1 (9%)
B_{12}	3 (27%)
Mg	3 (27%)
Se	4 (36%)
K	1 (9%)
Zn	2 (18%)
Cr	4 (36%)
Fe	3 (27%)
I	0

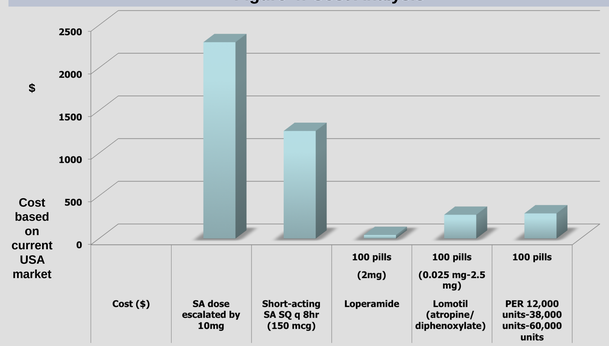
EFFICACY

Figure 3: Improvement in EPI Manifestations



Overall Response: 78%

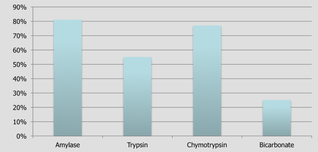
Figure 4: Cost Analysis



DISCUSSION

- SSAs both in preclinical studies and healthy volunteers, have shown to:
  - Inhibits the release of gastrin, cholecystokinin, secretin, motilin, and other GI hormones, such as GIP, VIP, insulin, glucagon
  - Decrease secretion of bicarbonate, water, and pancreatic enzymes into the intestine, subsequently decreasing intestinal volume
  - Decrease rate of gastric emptying
  - Reduces smooth muscle contractions and blood flow within the intestine, thereby allowing for a greater intestinal capacity
- SAAs was confirmed to be a potent inhibitor of stimulated human exocrine pancreatic secretion.
- The near maximal inhibitory potency of SSA was achieved at a dose of only 5 micrograms/h

Figure 5 : Effect of SSAs on Pancreatic enzymes



- Diagnosis of PEI is confirmed by two types of tests:
  - Direct test based on aspiration of the pancreatic contents during secretin or secretin-cholecystokinin/cerulein administration (only available in a few centers; invasive)
  - Indirect tests: CFA, Acid steatocrit, Fecal elastase 1, 13-C mixed triglyceride breath test, Fecal chymotrypsin, secretin-enhanced MRCP,
  - Nutritional status: Mg, Albumin, pre-albumin, retinol binding protein, ferritin, hemoglobin

CONCLUSIONS

- Our experience constitutes first study addressing PEI as a rare but serious complication of chronic use of SAAs.
- Although SAAs are used to treat diarrhea, paradoxically they can worsen diarrhea secondary to PEI.
- Early recognition and diagnosis of this under-diagnosed and under-reported side effect of SAAs can improve not only diarrhea and weight in these pts. but also can reduce cost of using short-acting SA and antidiarrheal.
- We believe this is an extremely topic of interest to internists, gastroenterologists, oncologists and surgeons, who need to be fully aware of this under-diagnosed toxicity associated with chronic use of SSAs.

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